

THE AMERICAN HEART JOURNAL



©Am. Ht. Assn.

ADVISORY EDITORIAL BOARD

| | |
|---------------------|---------------------|
| HENRY A. CHRISTIAN | JONATHAN MEAKINS |
| ALFRED E. COHN | JOHN H. MUSSER |
| LEROY CRUMMER | JOHN ALLEN OILLE |
| ELLIOTT C. CUTLER | STEWART R. ROBERTS |
| GEORGE DOCK | G. CANBY ROBINSON |
| JOSIAH N. HALL | LEONARD G. ROWNTREE |
| WALTER W. HAMBURGER | ELSWORTH S. SMITH |
| JAMES B. HERRICK | WM. S. THAYER |
| E. LIBMAN | PAUL D. WHITE |
| WM. MCKIM MARRIOTT | CARL J. WIGGERS |

FRANK N. WILSON

PUBLISHED BI-MONTHLY

UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

LEWIS A. CONNER.....Editor

Associate Editors

HUGH McCULLOCH

EVELYN HOLT

VOLUME VI
OCTOBER, DECEMBER, 1930
FEBRUARY, APRIL, JUNE, AUGUST, 1931

ST. LOUIS

THE C. V. MOSBY COMPANY



COPYRIGHT, 1931, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in U. S. A.

Press of
The C. V. Mosby Company
St. Louis

The American Heart Journal

VOL. VI

OCTOBER, 1930

No. 1

Symposium on Cardiovascular Syphilis

The papers which follow constitute the program of the meeting of the American Heart Association held in Detroit on June 24, 1930, and represent the first fruits of the efforts of the Committee for the Coordination of Investigation of that Association to encourage coordinated research in the various phases of cardiovascular disease.

SYPHILIS OF THE AORTA AND HEART*

HARRISON S. MARTLAND, M.D.
NEWARK, N. J.

PART I

ANATOMICAL TYPES ENCOUNTERED BY THE WRITER, AS MEDICAL EXAMINER IN CASES OF SUDDEN DEATH

UNTIL approximately ten years ago acquired syphilis as it affected the heart was thought to be chiefly a disease of the aorta and aortic valve producing aortic regurgitation, aneurysm or narrowing of the orifices of the coronary arteries.

Warthin is responsible for what is called the newer pathology of cardiac syphilis.

Warthin¹ in 1911 in a study of twelve cases of congenital syphilis affecting the heart, chiefly in infancy and childhood, concluded that the characteristic lesion is a diffuse or localized interstitial myocarditis in which *Spirochaeta pallida* can be demonstrated. In later life this may lead to the fibrous heart.

In 1914 after a study of 200 hearts in which spirochetes were found, he² stated that many cases of cardiac syphilis were not being recognized.

In 1918 he³ reported an incidence of 40 to 50 per cent of syphilis in his necropsy service, as compared to 6.5 per cent found by Symmers. He stated that the gumma was no longer the criterion for the diagnosis of syphilis but that milder, more diffuse, specific inflammatory processes occurred which eventually lead to fibrosis. Based upon the demonstration of spirochetes in various organs he estimated that about 30 per cent of the population was syphilitic.

*From the Pathological Department of the City Hospital, Newark, N. J., and the office of the Chief Medical Examiner of Essex County, N. J.

In 1925, based upon the study of eight hearts from cases of sudden death, collected over a period of twenty years, he⁴ attributes sudden death to an acute exacerbation of previously mild latent processes in the heart and aorta. The chief gross lesions were "patchy areas and streaked areas of pale, yellowish, grayish-yellow or gray color, without hemorrhage or congestion, scattered throughout the myocardium." He believes that such areas may easily be mistaken for anemic infarcts. Microscopic examination shows areas of old fibrosis (healed myocarditis), subacute infiltrations of lymphocytes and plasma cells between the muscle fibers, with angioblastic and fibroblastic proliferation and interstitial edema; more acute areas of interstitial edema with infiltration of lymphocytes, plasma cells, monocytes and a predominance of polymorphonuclears. Spirochetes were found, particularly in these more acute areas.

Clawson and Bell,⁵ in a study of 126 hearts associated with syphilitic aortitis collected over a period of sixteen years in an attempt to observe the anatomical changes in the valve, coronary arteries, myocardium and pericardium and to note the immediate relation of these changes to the cause of death, carefully followed Warthin's technique for the demonstration of these myocardial lesions.

In twenty-eight hearts showing aortic insufficiency they concluded that the main myocardial lesion was hypertrophy, and that little significance could be attached to any other gross or microscopic changes in the myocardium. Most of the small fibrotic areas were evidently a result of slight nonsyphilitic coronary injury, and were not of sufficient degree to be a factor in heart failure. Syphilis of the myocardium in these twenty-eight hearts was apparently rare, and when present was of insignificant degree. "With the exception of the hypertrophy, we found no anatomic change in the myocardium which seems sufficient to cause death." Spirochetes could not be found in any of the twenty-eight hearts.

In fifteen hearts from cases of sudden death attributed to closure of the coronary orifices, gross myocardial fibrosis was not observed, nor were infarcts, commonly found in cases of senile coronary sclerosis, present. Microscopic myocardial fibrosis was seen only in four cases. Its infrequency and the slight degree when present led them to think that it had little or nothing to do with cardiac failure in these hearts. Thirteen of these hearts were stained for spirochetes and none were found.

In twenty-three hearts with ruptured aortic aneurysms gross myocardial fibrosis was not present. Microscopic fibrosis to a slight degree was found about the aortic ring in four cases. No spirochetes were found in any of the cases.

The work of Clawson and Bell represents one of the most reliable attempts to duplicate Warthin's observations, and with negative results.

Many other investigators have experienced similar results. So difficult has it become to demonstrate the presence of spirochetes in lesions of the aortic valve and heart muscle, that many enthusiastic observers are now making a diagnosis of syphilis of the heart muscle on the presence of a few lymphocytes collected around a vessel, or in single rows of five or more. This is risky indeed, as lymphocytes are, notoriously, evidence of a chronic defense reaction in all sorts of disease, and even their perivascular arrangement is by no means pathognomonic of syphilis. Even the finding of isolated or few spirochetes in the heart muscle may mean nothing more than a historical landmark or a resting focus.

While Warthin's observations are of great pathological interest and are very difficult to refute, I am of the opinion that these myocardial lesions have been unfortunately greatly overexaggerated, and that they ordinarily are not extensive enough to produce serious cardiac embarrassment or to explain death. A tendency has been created, especially among clinicians to overemphasize the myocardial lesions and thus distract attention from the aorta.

Bearing in mind the fact that the supporters of the "newer" pathology of syphilis often attribute sudden death to specific myocardial lesions and their results, I have attempted to review my cases, observed as medical examiner of Essex County, over a five-year period, to formulate an opinion as to the correctness of their view.

This I believe is unique because it practically limits itself to bona fide cases of sudden death as encountered by coroners' physicians and medical examiners, and excludes all hospital and institutional deaths, and deaths occurring in a slower manner.

From June, 1925, to June, 1930, my office investigated 8,667 deaths, including homicides, suicides, highway accidents, falls, burns, poisonings, sudden deaths and those cases ordinarily handled by coroners' physicians. Autopsies were performed in 3,325 cases, or 38 per cent.

Of the total number of cases investigated 1,590, or 18 per cent, were cases of sudden death attributed to heart disease. These deaths occurred in the street, while at work, at home, etc., and when unattended by physicians. No hospital cases are included except those dead on arrival. The territory covered by the investigation was Newark and Essex County, having a population of 832,000.

Of the 1,590 sudden deaths due to heart disease, 300, or 18 per cent, were autopsied. The low percentage of autopsies was caused by the impossibility of removing many cases from their homes and places of death to the morgues, the history plainly indicating that death was due to natural causes.

Rheumatic heart disease was the cause of death in 60 cases, syphilis of the aorta and heart in 101, and arteriosclerotic heart disease in 139 cases.

In 101 cases of sudden death autopsied in which the cause of death was syphilis of the aorta and heart, aortic regurgitation was the predominating lesion in 36 cases, stenosis and atresia of the coronary ostia in 15 cases, aortic aneurysm in 38 cases, and unusual lesions, such as spontaneous rupture of aorta, dissecting aneurysm, military aneurysm, etc., in 12 cases.

TABLE I

STATISTICAL SUMMARY OF CASES INVESTIGATED BY THE MEDICAL EXAMINER'S OFFICE
DURING A FIVE-YEAR PERIOD (JUNE, 1925, TO JUNE, 1930)

| | |
|--|-------------|
| Number of cases investigated | 8,667 |
| Number of autopsies performed | 3,325 (38%) |
| Number of sudden deaths due to heart disease | 1,590 (18%) |
| Autopsies performed | 300 (18%) |
| Rheumatic heart disease | 60 cases |
| Syphilis of aorta and heart | 101 cases |
| Arteriosclerotic heart disease | 139 cases |

TABLE II

CLASSIFICATION OF ANATOMICAL TYPES OF SYPHILIS OF AORTA AND HEART
ENCOUNTERED IN 101 CASES OF SUDDEN DEATH

| | |
|--|----------|
| Aortic regurgitation | 36 cases |
| Stenosis and atresia of coronary ostia | 15 cases |
| Aneurysms | 38 cases |
| Unusual lesions | 12 cases |

The age, race and sex of these 101 cases are tabulated in Tables III and IV. It was possible to save for museum purposes about 60 hearts from these cases. Most of the hearts were studied histologically.

TABLE III

AGE, SEX, AND RACE OF 101 CASES OF SUDDEN DEATH FROM SYPHILIS OF AORTA
AND HEART

| DECADES | 10-20 | 20-30 | 30-40 | 40-50 | 50-60 | 60-70 |
|------------------------|-------|-------|-------|-------|-------|-------|
| Aortic regurgitation | 0 | 4 | 8 | 16 | 7 | 1 |
| 36 cases | | | | | | |
| Stenosis of coronaries | 0 | 2 | 5 | 5 | 3 | 0 |
| 15 cases | | | | | | |
| Aneurysm | 0 | 2 | 9 | 14 | 8 | 5 |
| 38 cases | | | | | | |
| Unusual lesions | 0 | 1 | 4 | 5 | 1 | 1 |
| Totals | | 9 | 26 | 40 | 19 | 7 |

TABLE IV

| | MALE | FEMALE | WHITE | COLORED |
|------------------------|------|--------|-------|---------|
| Aortic regurgitation | 30 | 6 | 16 | 20 |
| 36 cases | | | | |
| Stenosis of coronaries | 12 | 3 | 9 | 6 |
| 15 cases | | | | |
| Aneurysm | 33 | 5 | 17 | 21 |
| 38 cases | | | | |
| Unusual lesions | 9 | 3 | 4 | 8 |
| 12 cases | | | | |
| Totals | 84 | 17 | 46 | 55 |

The youngest case in aortic regurgitation was twenty-seven years of age; in coronary stenosis twenty-three years of age, and in aneurysm twenty-four years of age. The oldest individual dying from aneurysm was eighty years of age.

It will be seen from the above that in 101 sudden deaths due to syphilis of the aorta and heart, 55, or over one-half, were in colored people.

The total population covered in this series is 832,000, the colored about 60,000, or over 7 per cent. The greater negro frequency may be explained in two ways: first, the greater prevalence of syphilis among negroes, and second, the fact brought out by Libman that sudden deaths among hyposensitive people are more frequent than in normal and hypersensitive individuals.

Hyposensitive people may collapse and go into shock without feeling pain or other symptoms, while normal, or hypersensitive individuals may rest or seek medical advice at the onset of warning symptoms.

A. AORTIC REGURGITATION—

In the 36 cases of sudden death in which the predominant lesion was an aortic regurgitation, the typical widening of the commissures, deforming lesions of the aortic cusps with thickening of their free edges, and the hypertrophy and dilatation of the left heart formed the outstanding features of these hearts.

The largest heart weighed 1,160 grams, the smallest 360 grams, and the average weight was over 600 grams.

In none of these cases were outstanding myocardial changes noted other than hypertrophy. The little scarring seen in the myocardium was atrophic in type, and due to coronary injury caused by a superimposed arteriosclerosis.

In none of these cases was there an aortic stenosis or organic mitral lesion.

The deforming sclerosis of the aortic valve, with consequent hypertrophy and dilatation of the left ventricle, was of such gross extent that death seemed clearly explained without attributing it to any specific myocardial lesion, which lesion did not exist. It is a well-known fact that hearts of 500 grams or more in weight regularly fail without showing any other evidence of myocardial disease, aside from hypertrophy.

An associated narrowing of the coronary orifices was frequently seen but the outstanding feature of these hearts was the regurgitation.

B. CORONARY STENOSIS AND ATRESIA—

In the fifteen cases of sudden death, in which the predominant lesion was a narrowing of the orifice of one or both coronary arteries, the stenosis or atresia was always due to an encroachment by the syphilitic supravulvar sclerosis over the orifices of the arteries. This process was confined to the aortic wall and did not involve the arteries

distal to the aorta. The lesion was usually in the nature of a sclerotic scar. When there was a definite involvement of the aortic valve, with regurgitation, the heart was much larger than normal. Most of these cases, however, represent pure forms of coronary narrowing with syphilitic aortitis and without regurgitation. The heart, therefore, was normal, or only slightly enlarged.

The largest heart weighed 500 grams, the smallest 250 grams, and the average was about 380 grams.

The coronary arteries beyond the stenosis are usually normal in appearance, and rarely show much superimposed arteriosclerosis.

The myocardium in these cases was usually normal, or showed only slight, or moderate, hypertrophy, and no evidence of specific myocardial lesions was noted. In a few cases the heart was small and the muscle the seat of brown atrophy. I have spoken of this as an inanition atrophy, due to slow cutting off of a considerable amount of the blood supply.

Sudden death in these cases is more difficult to explain than in aortic regurgitation and aneurysm. It is not the same as in coronary sclerosis due to arteriosclerosis where the occlusion takes place rapidly. In syphilis there is a gradual narrowing often to the point of complete atresia. The condition found at autopsy must have existed for months and even years. Compensatory circulation had time to be established, either by way of normal anastomosing vessels, by increased anastomosis between left and right coronary after forty years of age, or by way of anomalous coronary circulation, or by way of the thebesian vessels.

If such a lesion as acute specific myocarditis of any extent could be demonstrated in these cases, the death would be easily explained. We have been unable, however, to find evidence of any extensive myocardial lesions. What then is the mechanism of the sudden death?

Attention has been recently called to the importance of the emotions of excitement, worry, fright, etc., in heart disease and sudden death. One case may be cited as of special interest.

A white man, aged fifty years, was driving his automobile and unwittingly passed a traffic signal. He was severely and unmercifully bawled out by the traffic officer and collapsed over the wheel, dying instantly. Complete atresia of the right coronary was found at autopsy and marked stenosis of the left, with typical syphilitic aortitis. The heart muscle was normal. The stenosis and atresia must have existed for months.

What was the final break that caused death in this case? His wife stated that he had never complained and appeared to be in good health the day he died. It is possible that fright may in the presence of serious chronic lesions, which the individual under ordinary circumstances may get along with in comfort, set up ventricular fibrillation. One of the patients in this series died during coitus.

In none of our cases of sudden death, in which at autopsy a syphilitic stenosis or atresia of the orifices of the coronary arteries was found, have we encountered any evidence of specific myocardial lesions sufficient to explain death, or even to influence the fatal outcome.

Any lesion in the myocardium, besides hypertrophy and occasional brown atrophy (inanition), has usually been interpreted as due to superimposed arteriosclerosis of the coronaries.

C. ANEURYSM OF AORTIC ARCH—

In thirty-eight cases of sudden death, in which a typical aneurysm of aortic arch was found, death is easily explained, as practically all the cases died from rupture.

The heart in the majority of these cases was only slightly or moderately enlarged. When it was greatly hypertrophied, there was always an added aortic regurgitation, which often was of more recent date than the aneurysm.

The muscle in none of these cases showed serious myocardial lesions that could not be explained by a superimposed arteriosclerosis. In none was there any evidence of specific myocardial lesions sufficient to influence the fatal outcome. As the direct cause of the death is usually rupture, it is obvious that no other factor played an important rôle in the death.

The largest heart in this series weighed 600 grams, the smallest 280 grams, and the average was about 400 grams.

D. UNUSUAL LESIONS—

In 101 sudden deaths from syphilis of the aorta and heart, unusual lesions were encountered in twelve cases.

Spontaneous rupture of the aorta occurred in five cases and was associated twice with bicuspid aortic valve. All the cases were attributed to syphilis of aorta, but it must be admitted that in this lesion the evidence of syphilis is often slight and difficult to determine with certainty. In none was there any narrowing of the isthmus. In two the rupture was complicated by an acute dissecting aneurysm.

Miliary aneurysms of the aorta with small blow-outs, usually into the pericardium, occurred in three cases.

Aneurysm of the right coronary artery was the cause of death in one case, rupturing into the pericardium. This was the only instance of gross syphilis seen in the coronary arteries beyond the aortic wall.

An intimal ulcer was seen in one case.

Negro, aged twenty-four years, collapsed in a lunch wagon. A small patch of syphilitic supravulvar sclerosis was found above the opening of the left coronary artery. This had ulcerated through the intima and had over it a thrombus composed chiefly of blood platelets which occluded the orifice of the coronary in a ball valve fashion, and had caused embolism into lumen of artery. Miliary gummata were found in the spleen, and an old penile scar.

A gumma of the left ventricle, on the interventricular septum, was the cause of one death.

A sudden death due to congenital syphilis of the aorta was seen in one case.

Negro boy, aged ten years, collapsed in street and died instantly. Extensive aortic syphilis indistinguishable from that found in acquired cases was found. The ordinary signs of congenital lues were found.

This is the only case of congenital syphilis of the aorta and heart encountered in this series.

E. SUMMARY—

1. Sudden death in chronic heart disease is commonly due to acquired syphilis of the aorta and heart. Syphilitic heart disease (33 per cent) is next in importance to arteriosclerotic heart disease (47 per cent), which is responsible for the greatest number of cardiac deaths. It exceeds rheumatic heart disease (20 per cent) as a cause of sudden death. Many of the rheumatic cases have a slower death from congestive failure or from superimposed subacute bacterial endocarditis.

2. Sudden death in acquired syphilis of the aorta and heart is almost always due either to an aortic regurgitation or to narrowing or atresia of the coronary arteries, or to the production of an aortic aneurysm, or to any combination of these three great dangers of syphilitic aortitis.

3. Sudden death is occasionally due to unusual lesions such as spontaneous rupture of aorta, dissecting aneurysm, gumma of heart muscle, miliary aneurysm, etc.

4. Specific lesions of the myocardium and of the coronary arteries beyond the aortic wall are infrequent, and, when they occur, are so slight in extent as to be of little practical importance. They rarely embarrass cardiac action, are insignificant in the production of cardiac failure and the slower modes of cardiac death, and are of little importance in explaining sudden death.

5. Congenital syphilis affecting the heart and aorta is so rarely encountered that it is of little clinical or pathological importance in the causation of sudden death in chronic heart disease.

PART II

CARDIAC SYPHILIS IS ESSENTIALLY A SUPRAVALVULAR AORTIC SCLEROSIS, ITS MAIN DANGERS BEING AORTIC REGURGITATION, STENOSIS OR ATRESIA OF THE OSTIA OF THE CORONARY ARTERIES AND AORTIC ANEURYSM.

ALL OTHER FORMS DESCRIBED IN MEDICAL LITERATURE ARE EITHER OF LITTLE CLINICAL IMPORTANCE, UNCOMMON, RARE, OR DO NOT EXIST

Acquired syphilis of the aorta and heart shows clinical manifestations usually fifteen to twenty years after infection, remaining undiscoverable, hence latent, and apparently harmless during that time.

It may remain latent throughout life and appear only as a historical landmark at autopsy, in the form of a small insignificant scar.

Genuine heart disease due to syphilis usually occurs between thirty-five and forty-five years of age. At least three-fourths of the cases show symptoms between the ages of thirty and fifty-five years. It is a little later than most rheumatic and a little earlier than most arteriosclerotic cases.

A. BIOLOGICAL DEVELOPMENT OF SYPHILIS OF AORTA AND HEART—

We know from the clinical failures to prevent syphilis by early excision of the chancre, backed by considerable experimental data, that there is an early invasion of the blood stream with *Treponema pallidum* even before the initial lesion appears.

The visible chancre appears as a local defense reaction at the original site of infection. The organisms multiply in the initial lesion in enormous numbers and are scattered over the body constantly by two important routes. The first is directly into the blood stream at the portal of entry. The second is a slower route by way of the lymphatics to the regional glands, where many organisms are undoubtedly destroyed by the phagocytic reticulo-endothelial cells lining the lymph sinuses.

The regional lymph nodes (for example the inguinal group) stop the infection temporarily by slowing it up, and the adenitis is purely a defense reaction. Many organisms survive, pass the first barrier of defense, and finally reach the thoracic duct. Eventually they are poured into the venous blood stream and taken to the right side of the heart.

Early treatment may destroy great numbers of spirochetes in and along the slower lymphatic route and in the initial lesion, but it is generally administered too late to destroy organisms which enter the blood stream direct from the portal of entry.

Later, when the secondary rash appears, there is a stage of very pronounced septicemia, or spirochetemia, when treponemata in large numbers invade every tissue of the body accessible to the blood stream. Many are taken to the myocardium.

The stage of septicemia does not last long. Even without treatment the normal organs of filtration and purification of the blood stream rapidly remove circulating treponemata from the blood, and the initial lesion has retrogressed or healed so that no further contamination of the blood stream takes place.

The purification of the blood-containing organs is further hastened by treatment, which is usually instigated before this time. Such early treatment, however, may be disadvantageous because the remaining spirochetes are driven into corners of the body inaccessible to the circulation. Treatment, therefore, must be persisted in over long periods.

As the stage of spirochetemia passes away the various organs attempt to rid themselves of the organisms by way of filtration, by phagocytic properties of reticulo-endothelial cells, and by way of lymphatic drainage into neighboring lymph nodes. This process may take years.

The spleen is greatly aided in freeing itself of organisms by its rich filtering structure, which permits stagnation and destruction by its reticulo-endothelial cells.

The lungs, which, on account of their very great capillary area have received a greater dosage of organisms than perhaps any other part of the body with the exception of the skin, must clear themselves in a somewhat different manner. Many of the organisms pass through the lungs' capillaries and reach the systemic circulation. Many are slowed up in the lungs, and because the *Treponema pallidum* is always attempting to leave the circulation for extravascular tissues in which they are less liable to injury, many escape into the interstitial portions of the lungs.

Numerous extravascular spirochetes may be further phagocytized by even the alveolar epithelium, which are probably mesothelial in origin and a part of the reticulo-endothelial system.

The lungs eventually rid themselves of the organisms by way of their lymphatics which drain to the peribronchial and regional nodes of the mediastinum. These become collecting stations, or reservoirs, for the storage of spirochetes. Here they are exposed to the phagocytic action of the reticulo-endothelial cells of the lymph sinuses.

In certain other organs, particularly the bones, lymph spaces of the skin, the nervous system and the heart muscle, the organisms are apt to rest and remain for years without attempt at removal, and with very little local reaction. In the heart, for instance, there can be no removal by lymphatic drainage, as lymphatic drainage from the heart muscle is scant. These locations are usually inaccessible to the blood stream, and, hence, to treatment.

Does cardiac syphilis begin at this stage? Do the organisms remain there in a latent condition, or do they set up a specific inflammation of the myocardium in the early stages of syphilis?

Warthin's observations lead him to conclude that in the second stage of syphilis there is a very active specific infiltration of the heart muscle.

Clinically, it is well known that various cardiac disturbances take place during the early stages of syphilis, such as tachycardia, bradycardia, arrhythmias and syncope. McLester⁶ states that the heart is easily excited and quickly exhausted. He is of the opinion that probably two-thirds of the patients with early syphilis show these functional disturbances. It is questionable whether this condition represents a true myocarditis, which he thinks is rare. Involvement of the

cardiac nerves, the vagus and sympathetic, as well as psychic influences, play a rôle in these disturbances. Brooks⁷ thinks that the production of clinical symptoms in this stage is very infrequent. Wile⁸ thinks that lesions of the heart are rare in early syphilis.

It is obvious that this question is very important. If there is a specific myocarditis in early syphilis, there is a foundation laid for a specific interstitial gummatous myocarditis, which some claim is so common in later syphilis.

I believe that it is possible to have a specific early myocarditis but that the lesion is very unusual. I also think that the heart muscle filters out many organisms during the secondary stage and they are eliminated with great difficulty. Those surviving often remain for many years without doing appreciable damage.

The finding, therefore, of a few spirochetes in the heart muscle in latent syphilis, perhaps surrounded by a few lymphocytes, may mean nothing more than an insignificant historical landmark. In a similar manner spirochetes may often rest in the skin of latent syphilitics, leaving no gross, and little microscopic evidence of their presence. Yet syphilis may be transmitted to rabbits by inoculation.

It is possible, therefore, that later gummatous myocardial lesions may have their origin in these early foci of specific myocarditis, or in the rests of treponema brought to the heart muscle during the early stages of bacteremia.

Most authorities have for years agreed that the earliest histologic lesions in syphilis involving the aortic root, will be found around the vasa vasorum in the adventitia, where there is a mantle of lymphocytes and histiocytes with an obliterating endarteritis.

It, therefore, seems reasonable to believe that the lesion in early aortic syphilis is a lymphatic extension of spirochetes from the reservoirs in the mediastinal lymph nodes by retrograde lymph flow into the perivascular spaces around the vasa vasorum.

Some years ago, Klotz⁹ cited the mediastinal factor in aortic syphilis. He furnished pathological observations, calling attention to the mediastinitis and periaortitis in syphilis of the aortic root and in aneurysms.

In addition, to support the mediastinal theory, there is roentgenographic evidence during life that around aneurysms in particular and widened aortas the seat of luetic aortitis there is a fuzzy border explained only by the periaortitis.

Stokes¹⁰ has further shown that during treatment of an aneurysm by specific drugs, many of the clinical symptoms, especially the pain, are relieved by the melting away of the mediastinal factor, while the physical signs of the aneurysm, such as size, pulsation and murmurs, often become intensified as a result of the relief of the surrounding tense barriers.

While I believe that the mediastinal factor is the important one in explaining the localization of the syphilitic process in the root of the aorta, it is still extremely difficult to prove.

It would be interesting to observe whether experimental transmission to rabbits could be made from mediastinal glands and periaortic tissues. Likewise more accurate data of the lymphatic and vascular supply of the aortic root are needed.

B. CONGENITAL SYPHILIS OF THE AORTA AND HEART—

It is a remarkable fact that with all the discussion about congenital cardiac syphilis the cases observed are very few in number.

Pediatricians in the examination of large numbers of children with undoubted congenital syphilis find almost none in which a diagnosis during life of syphilitic heart disease is possible. Clinicians encounter similar experience in older persons.

At autopsy the pathologist rarely finds any evidence of syphilis of the aorta and heart in cases having other earmarks of congenital syphilis, excluding stillbirths, as well as syphilitic infants dying in the first few months after birth. In the latter, spirochetes can be found in various organs, especially the liver, spleen, lung, osteochondral portions of long bones, and often in myocardium, yet such cases usually die not from heart lesions but from syphilitic meningitis.

In heredosyphilis the child is infected through the placenta, and an incalculable number of treponemata circulates throughout most of the organs, the number having no parallel in acquired syphilis. If the mediastinal theory is correct in the localization of acquired syphilis in aortic root, it might be possible that the aorta escapes in congenital syphilis, because the lungs of the fetus have escaped the large dosage of organisms that the other organs have received due to the fetal circulation not passing to any great extent through them.

In instances in which the lungs receive a large dose, a fatal pneumonia alba often occurs.

C. SYPHILITIC SUPRAVALVULAR SCLEROSIS—

The main and most important lesion in nearly all cases of acquired syphilis of the aorta is a supralvalvular sclerosis. Most of the other changes and phases of cardiac syphilis depend upon this lesion.

The earliest lesions are microscopic and occur around the vasa vasorum in the adventitia of the root of the aorta where there is seen a collection of lymphocytes and histiocytes, lying, probably, in the perivascular lymph spaces. Stained sections may show spirochetes in these areas, but usually they are found with difficulty. Small, miliumary gummata are formed in the adventitia.

There follows a secondary invasion of the media with consequent breaking up of elastica and weakening of the vessel wall. Obliterating endarteritis of the vasa vasorum is a common finding. Syphilis has

been usually considered a disease of the small arteries. The obliterating endarteritis is held by many to be a primary lesion indicating a hematogenous entrance of the syphilitic virus. Syphilis, therefore, being an endarteritis of the small vessels, it is obvious that it would appear at the place which contains the most small vessels, and this is the root of the aorta. This portion is also more richly supplied with lymphatics.

My interpretation of the endarteritis has been different, although it is not, as yet, subject to finality. Instead of assuming that the intimal changes indicate that the primary effect has been upon the interior of the vessel, hence a hematogenous infection, I have been in the habit of assuming that the vessels become obliterated as a part of a defensive reaction to an inflammation which starts around and external to them. It is an attempt to heal the surrounding gummatous area by limiting its blood supply, producing necrosis, etc.

The lesion develops to a stage at which it can be recognized with the naked eye. It usually begins in the aortic wall, just distal to the attachments of the aortic cusps. The earliest patch is often triangular, and situated just above the commissures connected with the aortic cusp forming the sinus of Valsalva, where the left coronary has its origin. The base of the triangle is usually pointed distally. There is a gray or slightly yellowish elevation with steep sharp edges, smooth on top, or marked by shallow furrows separating trivial secondary elevations.

The process spreads in a horizontal manner around the root of the aorta and distally as far as the mouths of the great vessels springing from the aortic arch. The orifices of the great vessels of the arch may often be narrowed to a marked degree. It may diffusely involve the whole aortic arch. Separate processes may develop in a similar manner in the thoracic or even abdominal aorta.

Histological study shows that the gummatous process, starting and most pronounced in the adventitia, has infiltrated the media, breaking up and pushing aside elastic fibers, and has gained access to the sub-intimal tissue of the aorta where there is less resistance to further infiltration.

I am not satisfied that the extension of the process follows the vessels down into the aortic cusps but rather am inclined to think it follows tissue spaces of least resistance and along perivascular lymph spaces.

The location of the triangular patches above the commissures, or their commissural origin, is best explained by the tug at these places during pulsatory dilatation of the aortic root, and the strain put on the valves and wall of the aorta when the ends of the free margins come together.

I speak of the whole process as a sclerosis because the lesion found at autopsy is in the nature of a deforming defect which has followed and is following a previous gummatous infiltration. Two groups, however, must be recognized. In one the process is distinctly softer, and histological examination still shows quite an active process. Such cases can be greatly benefited by treatment. In the other the gummatous process is subsiding so that the sclerosing deformities are more pronounced and predominate. This latter is the most frequent type seen at autopsy.

Symptoms and Physical Signs of Early Supraaortic Sclerosis.—The symptoms produced by early aortitis are chiefly dyspnea, which is mild, or slight on exertion, or comes in nocturnal paroxysms.

Precordial distress usually above the third rib is common.

Early physical signs are due to surrounding periaortitis and mediastinitis, which produce dilatation of the aorta without any intimal lesions being present.

The most characteristic and valuable physical sign is an accentuated second aortic sound, which is ringing and bell-like in quality. Such a finding in a man between thirty and forty-five years of age, without evidence of arteriosclerosis, hypertension or rheumatic heart disease, should force one to exclude syphilis by using every available means. The diagnosis of aortitis is difficult, and the disease is rarely recognized in the early stages. The blood Wassermann is often negative, and if we depend upon a serological diagnosis of cardiac syphilis we will miss some 30 per cent of cases.

In addition, a soft, systolic murmur may often be heard over the aortic area. This murmur is not transmitted and is probably produced by the increased rigidity of the aortic tube, since at this time no endocardial lesions may be present.

D. SYPHILITIC SUPRAAORTIC SCLEROSIS MASKED BY SUPERIMPOSED ATHEROMATOSIS AND ARTERIOSCLEROSIS—

One of the most confusing factors in the diagnosis of syphilis of the aorta and heart at autopsy is that the syphilitic lesion may be often masked by a superimposed atheromatosis, or arteriosclerosis, so that the underlying syphilis may be completely obscured.

This is so common that the greatest care must be exercised so that myocardial lesions due to coronary injury from the ordinary garden variety of senile arteriosclerosis are not mistaken for syphilis.

Pure, uncomplicated syphilitic lesions in the aorta are characterized by the presence of little or no fat and no calcification.

Infantile atheromatosis is very common. Yellowish plaques on the aortic cusp of the mitral are frequently seen in infancy. Atheromatous plaques in the coronary arteries may be seen as early as one year, and often in the second decade of life. The summit of cardiovascular life is about forty-five years of age when man has reached his biological

usefulness as far as reproduction of his race is concerned. After forty-five nature is trying to dispose of him rapidly as his usefulness is over. It is not only common to find evidence of atheromatosis and arteriosclerosis after the forty-fifth year, but unusual not to find it. Coronary thrombosis which is practically always due to localized arteriosclerosis of the coronary arteries is really a disease of early middle life and occurs most frequently around the summit of cardiovascular life, in contradistinction to the belief of many that it occurs later.

While we believe that cardiac syphilis forms only about 10 per cent of chronic organic heart disease, this assumption is based chiefly upon the finding of gross lesions characteristic of syphilis at autopsy. In the series of sudden deaths syphilis formed about 33 per cent of chronic organic heart disease producing death.

When we remember that many cases of cardiac syphilis may be obscured at autopsy by the arteriosclerotic process, it is evident that we miss many cases, and the incidence may be much higher.

Again, if we accept the criteria laid down by Warthin for the histological diagnosis of syphilis of the heart, the incidence will very rapidly increase.

It is quite impossible to state the frequency of severe syphilitic lesions of the heart causing death and the incidence of latent syphilis of the heart.

It is also important to state here that in uncomplicated syphilitic aortitis there is no marked hypertension. In this respect I have been for years of the opinion that syphilis played no rôle in the production of essential hypertension.

Furthermore, I am not willing to admit that persons suffering from syphilis of the heart and aorta are more liable to a superimposed arteriosclerosis.

E. SUPRAVALVULAR SYPHILITIC SCLEROSIS EXTENDING DOWN ON AORTIC VALVE WITH THE PRODUCTION OF REGURGITATION—

Aortic Regurgitation.—Aortic regurgitation is the first and most important danger of supravulvular sclerosis (syphilitic aortitis).

In a combined series of deaths, including hospital cases, aortic regurgitation occurred in about 60 per cent of cases of luetic aortitis which resulted in death.

In a series of 101 sudden deaths from cardiac syphilis, excluding hospital cases, aortic regurgitation was found as the cause of death in 36 per cent of cases. This shows that while the insufficiency is a very important lesion in sudden death a great many patients die a slower death from cardiac failure of the congestive type.

The aortic cusps are not primarily involved in acquired syphilis, but the regurgitation always results from a previously existing supra-

valvular lesion which has infiltrated to spread the cusps eventually, or to involve them in the syphilitic process.

The consecutive pathological events in the formation and development of aortic regurgitation, together with their clinical symptoms, may be discussed together.

Supravalvular Sclerosis.—The process in the aorta has already been discussed.

Extension to Aortic Cusps.—Extension of the syphilitic gummatous process through the media into the subintimal spaces producing the triangular patches, continues in the direction of the attachment of the aortic cusps, usually following the lines of least resistance, which is alongside of and between the fan-shaped subintimal fibers, the remnants of those fibers forming originally the aortic cusps.

The result is a pushing apart of the cusps at their attachments by the gummatous and sclerosing process. Sometimes the attachments of the cusps may be separated by at least 1 cm. Often, just a furrow exists between the attachments of the adjacent cusps, which are thickened and infiltrated. This widening of the commissures is the earliest sign of aortic regurgitation, and is practically the main factor in its production.

Clinical Symptoms and Physical Signs of Early Involvement of the Aortic Valve.—Extension to the aortic cusps causes a change in the systolic murmur. The murmur is thereby transmitted down the left border of the sternum, and as the cusps become involved, it becomes rough and harsh and transmitted into the vessels of the neck.

Widening of the aorta to perenssion, fluoroscopic and roöntgenographic examination may, or may not, be detected at this time. A slight hypertension is the rule in well developed, pure forms of aortic syphilis, the systolic pressure being 135 to 150 to 155. There is not sufficient hypertrophy of the left heart to detect usually at this period.

Involvement of the Aortic Cusps.—A continuation of the process down the attachment of the cusps takes place and often occurs across their free edges.

Fibroblasts lay down collagenous fibers. A hyalinized ball-like edge results. While, of course, considerable round-cell infiltration of a specific nature is seen in the free edges of the cusps near their attachment, the portions between the free edges are often remarkably clear of such specific changes. As many cases of regurgitation due to syphilis are seen which show no thickening of the free edges, but only widening of the commissures, I am inclined to interpret the thickening of the free edges as mainly mechanical in nature and due to strain produced by the regurgitant blood stream.

Dilatation of Aortic Ring.—The production of regurgitation by dilatation of the aortic orifice is not of much importance.

Aortic Valve Incompetent.—The distorted, thickened, rolled, and retracted aortic cusps with the widened commissures produce irreparable damage to the valve.

Subendocardial Fibrosis.—From trauma of the regurgitant blood stream, subendocardial fibrosis over the interventricular septum below the aortic valve, with the production of the so-called bird's nests, false bands and cusps, often takes place. The lesion is characteristic of a regurgitation but is not pathognomonic of syphilis. It is purely of mechanical origin and has nothing to do with any specific inflammation.

Hypertrophy of Heart, Especially Left Ventricle.—Hypertrophy of the muscle of the left ventricle is usually the only gross and microscopic finding of any importance. All other myocardial lesions are usually due to a superimposed arteriosclerosis. Occasional areas of specific myocarditis, especially in region of aortic ring may occur, they are usually small in amount, difficult of interpretation and of insignificant import.

Symptoms and Physical Signs of Fully Developed Aortic Regurgitation.—The symptoms and physical signs of a well-developed aortic regurgitation need not be repeated here.

Dilatation of Left Ventricle.—This represents about the last lesion in a well-developed case.

Death in Aortic Regurgitation.—Death in aortic regurgitation is in over half of the cases due to cardiac failure of the congestive type, therefore, a slow one.

Sudden death is common, occurring from acute cardiac dilatation or from cardiac failure of the anginoid type. The latter is especially liable to occur when there are associated lesions about the orifices of the coronaries, or a superimposed coronary arteriosclerosis.

Patients with well-developed aortic regurgitation due to syphilis do not usually survive a two-year period after the diagnosis has been made, even when properly treated. Many die in six to twelve months. Exceptional cases, however, may live for many years.

F. SUPRAVALVULAR SYPHILITIC SCLEROSIS WITH ENCROACHMENT ON THE ORIFICES OF THE CORONARY ARTERIES—

Coronary Stenosis and Atresia.—Narrowing of the orifices of the coronary arteries is the second important danger of supra-avalvular sclerosis (syphilitic aortitis).

In a combined series of deaths, including hospital cases, stenosis or atresia of the coronary ostia occurred in about 30 per cent of cases of syphilitic aortitis which resulted in death. As many of the aortic regurgitation cases also have narrowing of the coronaries, an exact grouping is quite impossible.

In a series of 101 sudden deaths from syphilis of the aorta excluding hospital cases, stenosis or atresia of the coronary orifices was

found to be the cause of death of some 15 per cent. Most showed little or no regurgitation.

The consecutive pathological events leading to narrowing of the coronary ostia with their symptoms are as follows:

Supravalvular Sclerosis: The primary lesion is of course the supravalvular sclerosis.

Stenosis and Atresia of Coronary Ostia: An important observation which attracted little attention in the causation of coronary narrowing in these cases was made by von Glahn,¹¹ who showed that often one or both coronaries may have their origin above the sinuses of Valsalva. Such high placed coronaries are a frequent congenital anomaly.

Martland¹² called attention in 1927 to the clinical importance of this observation and also to the comparative freedom of involvement of the sinuses of Valsalva in the syphilitic process.

As syphilitic supravalvular sclerosis usually starts in the portion of the aorta above a base line drawn through the upper limits of the attachments of the aortic cusps, coronary arteries which are congenitally situated above this line are especially liable to scarring of their ostia, while those normally arising in the sinuses often escape encroachment.

It is unusual for the syphilitic process to be seen in larger branches of the coronaries, and syphilitic coronary disease is practically limited to a narrowing, or atresia, of their orifices by the lesion in the aortic wall.

The heart in these cases is of normal size or only slightly or moderately enlarged.

The right coronary seems to be more liable to narrowing than the left.

When a coronary is completely obliterated so that its opening cannot be found, its exact location can be usually determined by opening the artery distal to the aortic wall. The vessel will usually be found quite normal in appearance and seems to escape a superimposed arteriosclerosis, as the walls have been saved from the wear and tear of arterial strain for some time.

G. SUPRAVALVULAR SYPHILITIC SCLEROSIS WITH PRODUCTION OF AORTIC ANEURYSM—

Aortic aneurysm is the third main danger of supravalvular sclerosis (syphilitic aortitis).

In a combined series of deaths, including hospital cases, aneurysm of the aorta occurred in about 10 per cent of the cases of syphilitic aortitis resulting in death.

In a series of 101 sudden deaths from cardiac syphilis, excluding hospital cases, aortic aneurysm was the cause of death in thirty-seven cases, or about 37 per cent.

The large increase in its incidence in cases of sudden death is easily explained by the mode of death, which is usually rupture.

For many years I have maintained that the heart in aortic aneurysm is not usually enlarged unless there is a coexisting aortic regurgitation.

The consecutive events in the production of aneurysm together with the symptoms may be discussed together:

Supravalvular Sclerosis.—The primary lesion is a supravalvular sclerosis which weakens the aortic wall so that an aneurysm may take place.

Failure of the Sclerosis to Involve the Aortic Valve.—In the formation of most aneurysms the most important factor is failure of the syphilitic sclerosing process to pass downward to the aortic cusps. At autopsy a great many specimens of aortic aneurysms will show little or no involvement of the aortic valve and no regurgitation. The heart is not much larger than normal.

As many aneurysms may exist for from ten to fifteen years, aortic regurgitation is often superimposed upon the lesion as a later development. Occasionally the aneurysm is so near the aortic ring or so large that it may cause regurgitation by dilatation of the ring alone, but this is not common.

What, then, is the mechanical factor that produces aneurysm? In uncomplicated syphilis there is only a slight or mild hypertension. The systolic blood pressure in aortitis ranges from 135 to 155 mm. In aneurysms the range is even lower. The production of aneurysm is more likely to occur if the aortic valve is competent, and the maintenance of a high diastolic pressure against the weakened aortic wall is possible.

Aneurysmal Dilatation.—From its inception the dilatation usually becomes progressively worse through the constant effect of the high maintained diastolic pressure.

Thrombosis.—The endothelial lining of the aneurysmal sac or dilatation is soon lost in places. Thrombus forms with organization and typical lamination. This has often been a protective influence, as many layers of laminated clot may act as a tampon. Even after rupture it may temporarily seal the small opening. The following case is of interest:

A white male, aged forty-five years, in apparent health had a terrific hemoptysis from which he collapsed. His recovery took about two weeks. Fluoroscopic examination showed a large aneurysm of the arch. He was living six months after the rupture. A sliding clot must have temporarily sealed the small blowout.

Pressure on Neighboring Structures.—This condition is common and causes many of the classical signs and symptoms of aortic aneurysm. They need not be discussed here. One interesting and unusual condition is the so-called aneurysmal phthisis of Osler. Pressure on a main bronchus may cause extensive suppurative bronchitis with abscesses of the lungs, etc. A septic type of temperature and scattered

physical signs of lung infection, with emaciation, may lead to the diagnosis of pulmonary tuberculosis.

Erosion of Adjacent Structures.—In this respect the erosion of the bodies of the vertebrae are of interest, particularly the resistance to erosion offered by the elastic intervertebral discs. These discs often remain intact, projecting out between the eroded bodies.

Symptoms.—The symptoms and physical signs of aneurysm are well known.

Death in Aneurysm.—As stated, sudden death in aneurysm is almost always due to rupture. If the orifices of the coronaries are also stenosed, death may be sudden from cardiac failure of anginoid type.

Slow death is due to failure of the congestive type, or a result of pressure on surrounding structures.

Occasionally death may result from embolism from contents of aneurysmal sac. Rupture into a tuberculous lymph node may disseminate tubercle bacilli producing a fatal miliary tuberculosis.

H. TREATMENT—

It is perhaps excusable for a pathologist to discuss treatment if he has formed certain opinions based upon anatomical observations.

Supravalvular Sclerosis.—Intensive treatment is desirable and should be given in early aortitis when there are no coronary, myocardial or cerebral signs or symptoms.

Of greatest importance before treatment is undertaken is the condition of the heart and coronary arteries. To determine whether the coronary arteries are involved electrocardiography is invaluable and should always be employed.

The patient must be questioned concerning cardiac pain and anginoid attacks.

Anginoid attacks occur chiefly in those cases in which there is a narrowing of the coronary arteries. As some 70 per cent of cases escape coronary narrowing this is the reason why anginal attacks are not seen with the same frequency as they are in arteriosclerosis.

Often the pain is a typical angina indistinguishable from that due to arteriosclerosis. In rare cases it may simulate an occlusion.

More frequently, however, the pain is not characteristic, and as many of the cases occur in hyposensitive individuals, especially in the negro, other symptoms may replace the pain.

Instead of typical anginal attacks, therefore, there may be only marked weakness, aerophagy, burning or gnawing pain in the epigastrium, symptoms which have little or no relation to exertion and are not relieved by nitroglycerine.

By intensive treatment we mean a period of previous desensitization of the latent syphilitic with mercury, bismuth, iodides, etc., in order to avoid a Herxheimer reaction. This is followed by the administration with great care, of a course of intravenous arsphenamine or any

of its derivatives followed by intramuscular injections of bismuth, etc., and such a course repeated after suitable rest periods according to the progress of the individual case.

If the aortic lesions happen to be soft and predominantly gummatous, which some are, almost a complete healing may be obtained, saving the patient from coronary stenosis, regurgitation, aneurysm, or any combination of these lesions.

If the aortic lesion is more sclerotic in type, which the majority are, the melting away of the sclerotic process can never be completely accomplished, but the disease can undoubtedly be arrested.

With careful treatment cases may often be practically cured provided the lesion has not reached the openings of the coronary arteries. The sclerosis at least stands a good chance of being changed from a slowly progressive disease with a fatal outcome into a stationary one not incompatible with many years of life. A *restitutio ad integrum* is impossible but further progress of the disease may be checked.

Aortic Regurgitation.—Intensive specific treatment is of little value and is distinctly dangerous. If it does not kill the patient, it gives little relief or benefit.

If cardiac failure of the congestive type is present, specific treatment is out of the question, as cases should not be treated during decompensation. Rest, digitalis, and the orthodox treatment for cardiac failure are to be employed.

Mild preparatory treatment with bismuth, iodides, etc., followed by the judicious use of neoarsphenamine in small doses often prolong life. But the results are less brilliant than in any other form of cardiac syphilis. It must be remembered that the patient is suffering from an irreparable, sclerotic valvular defect and that very little pathological basis exists to warrant any wonderful therapeutic results.

Coronary Stenosis.—If in cardiac syphilis narrowing of the coronary arteries is diagnosed with a fair degree of certainty from the clinical history of syphilitic anginal attacks and electrocardiographic evidence, antisymphilitic treatment is usually contraindicated. If treatment is decided upon, the greatest care must be taken to prepare the latent syphilitic properly for arsphenamine or its derivatives.

Too early an injection may be followed by a Herxheimer reaction with edema of the coronary orifice and sudden death, or a severe attack of cardiac pain with all its consequences.

Intensive use of arsphenamine or its derivatives may cause too rapid healing of the syphilitic process and leave a stenotic scar. The effects of a healed lesion may leave the patient in a worse condition than before treatment (therapeutic paradox of Stokes). The following case is cited as an example:

Male, white, aged forty-three years, who was an old luetic for many years, developed a syphilitic laryngitis with almost complete loss of voice. Blood Wasser-

mann negative. Examination failed to show any evidence of involvement of the nervous system, the heart or other organs. He was in good physical condition. No electrocardiographic examination was made. He was started at once without any great amount of preparation, because of the desirability of rapidly clearing up his throat, with intensive arsphenamine treatments. Just after completing his first course he had an attack which resembled a coronary occlusion, with typical drop in blood pressure, shock, extreme and prolonged pain and sudden enlargement of liver. He gradually recovered and had two other similar attacks of less severity. Since this time he has been in fair health except for slight dyspnea. Since his initial attack five years ago his electrocardiograms have shown T-wave negativity in Lead I, abnormal QRS complexes, low amplitude in Lead II, and left axis deviation.

In this case there seems to be little doubt that the orifice of the right coronary was too rapidly healed by intensive treatment, and he has developed a stenosis or complete atresia of the artery due to a healed lesion, the slow course of which allowed compensatory circulation to take place.

Aneurysm.—Many cases of aneurysm, especially those in which there is considerable periaortitis and mediastinitis may be greatly benefited by specific treatment.

The patient should always be prepared as in case of any latent stage of syphilis. Then small doses of the arsphenamines, or their derivatives, carefully administered, with no attempt to cure the disease, may relieve the main symptom, pain, by melting away the surrounding syphilitic periaortitis. Aneurysms, with considerable fibrotic changes, are not so benefited. The treatment is dangerous in aneurysms with thin walls. While the pain is often relieved, the physical signs may increase because of a relief of the surrounding syphilitic inflammation.

In general the effects of antisyphilitic therapy are not altogether favorable, especially when the disease has reached the more advanced stages. Prevention is better than an attempted cure. If syphilis is more effectively treated in the early stages, many cases of aortitis could be prevented.

I. UNUSUAL LESIONS—

Spontaneous Rupture of Aorta.—Spontaneous rupture of the aorta without any relation to trauma is often, but not always, due to syphilis. It is of great medicolegal importance, because the gross evidence of syphilis is often very slight, the aorta and aortic valve being unusually normal in appearance. Frequently, however, histological examination in the region of the tear will verify the diagnosis of syphilis.

The location of the tear is generally about 2 to 3 cm. above the aortic cusps, or in the region of the ductus Botalli. At these locations fixed points exist between the ascending aorta and the pulmonary artery and at the site of the obliterated ductus arteriosus.

These spontaneous ruptures do not always kill and can sometimes be identified at autopsy as a healed scar.

In addition, many of the dissecting aneurysms found at autopsy and appearing as the double barreled aortas, the false tube being entirely lined by ingrowing intima, probably had their origin years before in a spontaneous tear.

The following cases are of interest in connection with the foregoing:

A negro, aged forty-five years, in apparent health, collapsed on the street and was removed to hospital, dying en route. The whole time consumed from the fall on the street to his death was not over thirty minutes. At autopsy a spontaneous rupture of the first portion of the aorta was found with a dissection of the greater part of the adventitia from the entire aorta down to the right femoral artery with tearing into the right and left common iliac arteries and a reestablishment of the blood stream. A final break into the pericardium caused death and prevented a chronic dissecting aneurysm. Many of the intercostal and lumbar arteries were torn completely across between the media and adventitia.

There is no question that in this case almost the entire adventitia was peeled off the aorta in less than thirty minutes.

A white woman, aged forty-six years, collapsed while at work. She was removed to hospital where she lived six hours in a condition of profound shock. At autopsy a spontaneous rupture of the first portion of the aorta was found with a dissecting aneurysm which reentered the aorta just below the innominate artery. A rupture into pericardium caused death.

It is possible, therefore, that many chronic dissecting aneurysms are not of slow progressive origin, but that the greatest extension of the aneurysm takes place at the time of the spontaneous rupture. With reestablishment of the circulation the strain is relieved, death prevented, and healing over a longer period of time takes place.

Miliary Aneurysm.—Small aneurysms of the aorta with minute blow-outs usually into pericardium are occasionally seen. They are apt to occur in the first portion of the aorta, frequently near the sinus of Valsalva, or in them.

Other Lesions.—Other lesions than those described above are exceedingly rare and of little importance.

SUMMARY

1. Acquired cardiac syphilis is essentially a supravulvular sclerosis which may manifest itself in one or more of the following ways:

(a) As small isolated patches of sclerosis in locations doing little damage (historical landmarks).

(b) As larger areas of sclerosis which become confluent and convert the aortic arch into a thickened, rubbery tube.

(c) As triangular patches of sclerosis which infiltrate between the commissures of the aortic cusps causing regurgitation.

(d) By extension of the scarring process over the coronary ostia with narrowing or complete atresia of one or both arteries.



Fig. 1.—Aortic regurgitation. First, most frequent and important danger of syphilitic supravulvular sclerosis (syphilitic aortitis). Occurs in about 60 per cent of syphilitic aortitis which result in death (combined hospital and medical examiner's statistics).

About 36 per cent of cases of sudden death due to syphilis of aorta and heart show regurgitation as the predominating lesion (medical examiner's statistics).

SUMMARY:

1. Always a secondary extension from a syphilitic aortitis.
2. Widening of commissures by infiltrating, sclerotic process is the important lesion producing the regurgitation.
3. Thickened free edges of aortic cusps are usually mechanical in origin.
4. Aortic regurgitation is often combined with narrowing or atresia of the coronaries, and it is sometimes superimposed upon an old aortic aneurysm.
5. Heart nearly always shows marked hypertrophy and often dilatation, especially of the left ventricle.
6. Main myocardial lesion is hypertrophy. Seen on gross and microscopic examination. Other lesions are infrequent and of no great significance.
7. The irreparable sclerotic lesion is not as a rule favorably influenced by specific treatment.
8. Sudden death is due to acute dilatation or to an anginal type of failure when the coronaries are involved. When death is delayed it is usually due to failure of the congestive type.
9. As a rule patients do not survive a two-year period after the diagnosis is made. Many die within six to twelve months. Exceptional cases may live for many years.

Case CME, 9053.—Male, aged 43 years. Colored actor, sudden death while reading his lines.

The heart weighed 1160 grams. Typical, triangular patches of supravulvular sclerosis with extension to the aortic cusps may be noted. There is not much thickening of the free edges of the cusps, the main lesion being the commissural widening.

The heart muscle showed enormous hypertrophy, and no specific lesions were seen on microscopic examination. The right coronary has a high origin and shows beginning encroachment on its orifice.

A probe is inserted in the orifice of the left coronary.



Fig. 2.—Aortic regurgitation, (1) CME, 2543. Male, white, aged thirty-five years. Sudden death in moving picture house. The typical triangular patches of sclerosis with extension to the aortic cusps, widening of the commissures, thickening of free edges, retraction of cusps and false bands on interventricular septum, may be noted. The coronaries, although their orifices are high, have escaped encroachment by the syphilitic process. The sinuses of Valsalva are free. The orifice of the right coronary is on the edge of a sclerotic patch but it is not yet stenosed.

(2) CME, 4644. Male, colored, aged forty-six years. Sudden death in physician's office. Same as 1. There is beginning encroachment on orifice of right coronary which is situated slightly above base line.

(3) CME, 4813. Male, colored, aged thirty-eight years. Sudden death on street. The heart shows aortic regurgitation combined with coronary stenosis and atresia. There is fusion of the triangular patches forming a horizontal band across first portion of the aorta and producing complete atresia of the right coronary, the orifice of which is an atresed dimple 1.5 cm. above the base line. There is marked rolling of the free edges of the cusps.

(4) CME, 4532. Male, white, aged fifty-seven years. Sudden death while at work. The heart shows aortic regurgitation with marked superimposed arteriosclerosis. The aortic cusps are retracted, shrunken with marked rolling of their edges. The syphilitic process in the aorta is almost entirely obscured by the arteriosclerosis.



Fig. 3.—Stenosis and atresia of coronaries, second main danger of syphilitic supra-valvular sclerosis (syphilitic aortitis). Occurs in about 30 per cent of syphilitic aortitis resulting in death (combined hospital and medical examiner's statistics). This percentage, however, includes many cases of aortic regurgitation with combined lesions.

About 15 per cent of cases of sudden death due to syphilis of aorta and heart show coronary stenosis and atresia in more or less pure form.

SUMMARY:

1. The process is always a narrowing, often to a complete atresia, of one or both arteries, due to encroachment upon their orifices in the aortic wall by the syphilitic process. Syphilis of larger and even smaller branches of the coronaries is rare and of little clinical or pathological importance.

2. If the coronary orifices are congenitally high above a base line drawn through the upper attachments of the aortic cusps, they are much more liable to narrowing than if they arise normally in the sinuses of Valsalva.

3. The heart is usually normal in size or slightly enlarged in the pure forms of this lesion. The muscle is quite normal in appearance and usually shows no evidence of any specific myocardial lesions. Occasionally an inanition atrophy similar to brown atrophy is seen.

4. As the narrowing or atresia takes a long period of time in its development, compensatory circulation is often established.

5. Sudden death is difficult to explain on account of the long duration of the stenosis. Physical strain, fright, emotions, etc., seem to play an important rôle. Syphilitic angina usually occurs in this type of case and not in other forms of cardiac syphilis. It is usually anginoid with atypical symptoms, but sometimes resembles the angina of arteriosclerosis, and even an occlusion in rare instances.

6. Specific treatment in these cases is usually contraindicated, because of the danger of a Herxheimer reaction or too rapid healing causing a therapeutic paradox.

Case, CME, 5858—Male, white, aged forty-nine years. Sudden death on street. The heart shows extensive, diffuse supra-valvular sclerosis with complete atresia of the left coronary, the orifice of which cannot be found, and marked stenosis of the right coronary. Both arteries have their origin above the base line.

6. McLester, James S.: Textbook of Medicine, Cecil, Philadelphia, 1928, p. 408, W. B. Saunders Co.
7. Brooks, Harlow: Treatment of Syphilis of the Heart, Interstate P. G. M. Assn., Oct. 12, 1925.
8. Wile, Udo J.: AM. HEART J., October, 1930.
9. Klotz, Oscar: Modern Clinical Syphilology, Stokes: Philadelphia, 1928, p. 830, W. B. Saunders Co.
10. Stokes, John H.: Modern Clinical Syphilology, Philadelphia, 1928, pp. 830, 831, W. B. Saunders Co.
11. von Glahn, William C.: Coronary Disease and Infarct of the Heart, Proc. N. Y. Path. Soc. 23: 107, 1925.
12. Martland, H. S.: Cardiac Syphilis (Syphilitic Aortitis), J. M. Soc. N. J., 24: 689, 1927.

DISCUSSION

Dr. R. W. Scott, Cleveland, Ohio.—I am interested in this material. I would like to ask Dr. Martland in regard to those cases in which arteriosclerosis obscures the lesions of aortic syphilis, whether or not he believes that widening of the commissure affords sound evidence for the presence of syphilis. We agree with his observation concerning involvement of the valve, especially the middle portion. We have not demonstrated syphilis in this position, and I think that the thickening of the midportion of the valves is due to eversion during diastole.

Dr. H. S. Martland (closing).—I think the widening of the commissure is so characteristic of syphilis as to be almost sufficient for diagnosis.

(e) By weakening of the aortic wall and production of aneurysm. This is especially likely to occur when the aortic valve remains competent.

(f) By any combination of the above.

2. We speak of the process as a sclerosis because the lesion found at autopsy is a deforming defect which has been following previous gummatous infiltration. In a somewhat similar manner we speak of the chronic valvular defects of rheumatism. The process in syphilis never heals completely. In some cases the lesion may remain distinctly gummatous and the involved areas soft. These are more favorable for treatment than the deforming sclerotic cases.

3. Syphilis involving other portions of the heart is unusual and is of no great clinical or pathological importance.

CONCLUSIONS

1. From a clinical and pathological standpoint, I believe that we should regard syphilis of the aorta and heart as an acquired disease (congenital cases being infrequent) developing insidiously and showing symptoms years after the initial infection.

2. It is possible to recognize clinically and to diagnose an early aortitis, an aortic regurgitation, a narrowing of the coronary ostia, an aneurysm, or any combinations of these lesions. Treatment and prognosis should be based mainly upon such recognition.

3. The myocardium in syphilis is frequently normal. When the aortic valve is involved, the main myocardial lesion is hypertrophy. Inanition atrophy is occasionally encountered. Specific lesions of the myocardium are infrequent, and, when they occur, are so slight in extent as to be of little practical importance.

4. It is safer and better to assume that the coronaries distal to the aortic wall are usually normal in pure, uncomplicated syphilis, and that coronary occlusions, anemic infarcts, necrosis of heart muscle, replacement fibrosis, aneurysms of ventricular walls, and fibrous myocarditis are almost entirely due to coronary injury dependent upon an arterio-sclerotic process and have nothing to do with syphilis. That rheumatism and other infections may also produce forms of interstitial myocarditis is obvious. But it appears that syphilis does not play an important rôle in the production of such lesions.

REFERENCES

1. Warthin, A. S.: Congenital Syphilis of the Heart, *Am. J. M. Sc.*, 141: 398, 1911.
2. Idem: Primary Tissue Lesions in the Heart Produced by *Spirochaete Pallida*, *Am. J. M. Sc.*, 147: 667, 1914.
3. Idem: The New Pathology of Syphilis, *Am. J. Syphilis*, 2: 425, 1918.
4. Idem: Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis, *AM. HEART J.*, 1: 1, 1925; *J. A. M. A.*, 84: 1597, 1925.
5. Clawson, B. J., and Bell, E. T.: The Heart in Syphilitic Aortitis, *Arch. Path. & Lab. Med.*, 4: 922, 1927.

THE GROSS PATHOLOGY OF THE HEART IN CARDIOVASCULAR SYPHILIS

JAMES G. CARR, M.D.
CHICAGO, ILL.

THIS study covers cases from the records of the Cook County Hospital in which a diagnosis of syphilitic aortitis was made at autopsy. Except for 8 cases, the full clinical records of which for one reason or another could not be obtained, all of the cases are here included in which syphilitic aortitis was found during 1929.

The diagnosis of syphilitic aortitis was based on accepted macroscopical and microscopical findings of this condition. Syphilitic aortitis is characterized grossly by its appearance and location. The intima of the aorta shows an irregular wrinkling, fine or coarse, with irregularities of the surface, the result of elevations and depressions produced by scattered areas of inflammatory fibrosis. The intima is no longer smooth, permitting the light yellow media to shine through; the patches of aortitis are whitish in color. This process begins about one centimeter above the aortic ring, and is usually most marked in the ascending portion of the aorta, though it frequently involves the entire thoracic aorta. Occasionally the whitish plaques and wrinkling are found in the abdominal aorta, even as far as the division into the common iliacs. The process may be quite marked about the mouths of the main vessels arising from the arch and the intercostal arteries, but it rarely extends along the course of these vessels.

Histologically, the process is characterized particularly by the presence of perivascular infiltration of the vasa vasorum, which begins in the adventitia but develops also in the media, and by the new formation of capillaries extending into the media. Later, perivascular areas of connective tissue with round cells and plasma cells may be found, and scar formation within the media, the retraction of which is responsible for the wrinkling and furrowing of the intima. The perivascular inflammation and formation of new capillaries are of most importance in the diagnosis. In the series studied, the anatomical diagnosis, if in any way questionable, was confirmed by microscopic examination. In the last five months of the year, after this study was planned, the diagnosis was not made by the pathologist, Dr. Jaffe, or his assistants unless confirmed microscopically.

The differentiation must be made from loss of elasticity, atheromatosis and aortitis of nonspecific origin. Simple loss of elasticity is characterized by fine wrinkling, longitudinal and parallel as compared to the coarser wrinkling with the marked irregularity of syphi-

lis. The presence of atheromatosis is characterized by plaques, hyaline and fatty atheromatous ulcers, and calcification. Fatty plaques, ulceration, and calcification are not a part of syphilis alone. Atheromatosis is a simple degenerative process, unassociated with inflammatory changes in the adventitia or media. There may be degeneration of the media without newly formed capillaries or cellular infiltration. The ultimate decision is with the microscope. In younger individuals the picture of syphilitic aortitis is usually clear; the intima has lost its smoothness, shows irregular wrinkling and puckering and the color changes from light yellow to white. In older individuals the presence of atheromatosis clouds the picture and makes microscopical examination imperative for diagnosis. The frequent coincidence of aortic syphilis and atheromatosis is responsible for the difficulties encountered in the attempt to estimate the clinical significance of either process.

The differentiation of syphilitic aortitis from rheumatic or nonspecific aortitis is difficult; in both conditions the perivascular infiltration is found, but in the rheumatic type this is more strictly confined to the adventitia and probably does not invade the media beyond its outer third, that part of the media adjacent to the adventitia. The diagnosis, however, rests largely upon the history and stigmata of syphilis in one group, the history and presence of other signs of rheumatic cardiac disease in the other. It is very difficult to differentiate the etiology of perivascular scars.

One hundred and nineteen autopsy reports were studied. In 19 instances the weight of the heart was less than 300 grams. Forty-four of the hearts weighed between 300 and 450 grams, and 51 over 450. In 5 instances the exact weight of the heart was not recorded. The largest heart weighed 1,060 grams. This was from the body of a man sixty-six years old. Another heart weighed 1,000 grams, and 8 weighed over 700 grams each. The myocardium presented no characteristic findings. Twice fresh infarctions were found and six times old scars, probably of vascular origin. One of these had resulted in a cardiac aneurysm and another had caused the replacement of about the upper one-third of the ventricular septum with a fibrous scar. Parenchymatous degeneration was described 14 times; in 10 instances this was associated with some severe infectious disease; once with carcinoma; once with atrophic cirrhosis; once with primary contracted kidney, and once with marked coronary sclerosis associated with primary contracted kidney. Cloudy swelling was described four times, twice with generalized tuberculosis.

In 4 instances there was partial obstruction of one of the larger branches of the coronary circulation; once an occlusion was complete. In 49 instances it was noted that the coronary vessels were narrowed or contained numerous plaques. The coincident occurrence of gener-

alized arteriosclerosis with the syphilitic changes in many of these cases makes it impossible to separate the two factors in the consideration of coronary disease. In 10 instances, however, the reports justify the conclusion that the typical wrinkling of syphilitic disease had involved the aortic intima about the coronary orifices. These figures are somewhat less than Dr. Jaffe anticipated. One striking statement is found in the report of an autopsy upon the body of a woman of twenty-four years. "Orifices are narrowed with wrinkling about them."

The cardiac hypertrophy as shown by the weight of the heart may be further illustrated by the measurements of the ventricles. Kaufmann quotes Krause as authority for the statement that the normal thickness of the right ventricle is from 5 to 7 millimeters; that of the left from 11 to 14. In this series, the thickness of the left ventricle was more than 14 millimeters (the maximum normal just quoted) in 87 instances; in 61 of these, this measurement was more than 18 millimeters; of 38 hearts in which the thickness of the left ventricle was more than 20 millimeters, 28 weighed more than 450 grams. In this same group aortic insufficiency was diagnosed anatomically 12 times, primary contracted kidney 6 times, secondary contracted kidney twice, and eccentric hypertrophy with benign arteriosclerosis of the kidney 5 times. (This last term as used in the pathological report appears to be most closely related to the condition regarded clinically as hypertensive heart disease.) In the whole series the thickness of the right ventricle was more than 7 millimeters, only 10 times; in all of these the left ventricle gave measurements above the maximum cited, although in one case in which death had resulted from chronic pulmonary tuberculosis, the left ventricle was only 15 millimeters thick; of the other 9, 5 were cases in which the total cardiac weight was over 600 grams. In one instance death was the result of malignant endocarditis of the pulmonary valves, in another of mesothelioma of the pleura. Of the 10 cases of right ventricular hypertrophy, one-half were a part of an extreme cardiac enlargement, and 3 were the result of a chronic disturbance of the pulmonary circulation.

In a number of instances small pericardial effusions were noted. In 19 cases more than 100 c.c. of fluid was found. In 8 of these there was decompensation with general anasarca; the amounts of fluid found varied from 100 c.c. to 300 c.c. Four times the cause of death was uremia, due to contracted kidney, and once, uremia resulting from ascending infection of the urinary tract. In one of these five, and in another case of contracted kidney where the pericardial effusion was small, fibrinous pericarditis was present. Twice, serous effusions were found with aneurysm; once a hemorrhagic effusion following rupture of an aneurysm into the pericardial sac. Once bronchopneumonia was the cause of death, once mesothelioma of the pleura, and in another

ease in which the largest effusion was found, 700 c.c. of the purulent fluid, a malignant endocarditis of the pulmonic valves was present. From the standpoint of gross pathology, syphilis is, at least, an infrequent cause of pericardial disease.

TABLE I

| | |
|---|----|
| Cases 119. | 19 |
| Weighing less than 300 grams | 44 |
| Weighing between 300 and 450 grams | 51 |
| Weighing more than 450 grams | |
| Myocardium (no characteristic findings) | |
| Fresh infarctions | 2 |
| Old scars | 6 |
| Parenchymatous degeneration | 14 |
| (Associated with severe infection, 10) | |
| Partial coronary occlusion | 4 |
| Complete coronary occlusion | 1 |
| Coronary vessels narrowed or showing numerous plaques | 49 |
| Syphilitic wrinkling involving coronary orifices | 10 |
| Pericardial effusion (more than 100 c.c.) | 19 |
| (All attributable to some intercurrent disease) | |
| Aortic aneurysm | 13 |
| (Involving heart, 2) | |
| Aortic regurgitation | 24 |

Aortic aneurysm was present 13 times; only twice was the heart involved. Once a small aneurysm ruptured into the pericardial sac. Once there was found an aneurysmal outpouching of a sinus of Valsalva. All of the aneurysms occurred in male subjects.

The diagnosis of aortic regurgitation was based on anatomical findings, not on the water test. The criteria were thickening, adhesion, and shortening of the commissures and thickening of the free edges of the leaflets with retraction. In one case of aortic insufficiency, marked dilatation of the aortic ring was noted. The anatomical diagnosis of aortic insufficiency was made twenty-four times.

From another point of view, these findings fall rather easily into the three groups already mentioned. In the first group, including those with hearts less than 300 grams in weight, there were 19 cases; of these, 18 died of some intercurrent disease. Under this term are included all cases in which death was due to some cause other than cardiovascular disease. Two presented anatomically the findings of aortic regurgitation; one of these had presented the clinical findings of cardiac disease; the other died of bilateral renal suppuration. While reference was made to systolic murmurs in some instances the clinical records indicate that in the 18 cases serious thought of cardiac disease had not been entertained. In 2 of the 19 cases the blood pressure had been over 160. Ten of the group were females. This might be expected in a group based on the small weight of the heart. The average age at death in this group was 47.9. Marked coronary sclerosis was found 5 times.

The second group includes hearts weighing between 300 and 450 grams (not more than 50 per cent above the commonly accepted normal); there were 44 of these. In 21 cases death was the result of some intercurrent disease; in 6 of these, cardiac disease had been recognized

TABLE II

| | TOTAL | AVERAGE AGE | DEATH FROM INTER- CURRENT DIS- EASE | BLOOD PRES- SURE OVER 160 | ANEU- RYSM | AORTIC INSUF- FICIENCY | MARKED CORO- NARY SCLE- ROSIS |
|---|-------|----------------|--|---------------------------------------|---------------|------------------------------|---|
| Group 1. Weighing less than 300 grams | 19 | 47.9 | 18 | 2 | 0 | 2 | 5 |
| Group 2. 300-450 grams | 44 | 50.0 | 21 | 9 | 8 | 3 | 8 |
| Group 3. More than 450 grams | 51 | 48.0 | 8 | 28 | 5 | 19 | 18 |

clinically. In this group there were 8 aneurysms and 3 cases of aortic regurgitation. In 9 cases (20.4 per cent) the blood pressure had been 160 mm. or above.

In this group, primary contracted kidney was found once; apparently 3 cases diagnosed anatomically as renal arteriosclerosis with eccentric hypertrophy of the heart had been regarded clinically as hypertensive cardiac disease. In 8 instances marked coronary sclerosis was noted; in one of these there was partial occlusion of one coronary orifice. The record of this case contains this statement, "distinct wrinkling, especially about the coronary orifices." In this group the average age was fifty years.

In the third group, including hearts of more than 450 grams in weight, there were 51 cases; the average age was forty-eight years. In 8 cases, death was due to intercurrent disease; in 3 of these the presence of cardiac disease had been diagnosed. Aneurysm was present 5 times. Aortic regurgitation was found anatomically in 19.

The percentage incidence of aortic regurgitation was 37.2, as against 11.4 in the second group and 10.5 in the first. In 13 instances, the clinical records of those with aortic regurgitation had shown the blood pressure above 160. In 28 of the entire group the pressure had been over 160, a percentage incidence of 57.1 as against 20.4 already cited for the second group and 11.7 for the first group. Primary contracted kidney was present 6 times. Marked coronary sclerosis was noted 18 times; in 3 instances there was partial, and in one, complete closure of a main branch of the coronary circulation.

CONCLUSIONS

1. Except for the predominant left ventricular hypertrophy which resembles that of essential hypertension, the gross myocardial changes associated with syphilitic aortitis are not characteristic.

2. The incidence of myocardial degeneration as a result of syphilitic involvement of the coronary circuit is not great. The frequent occurrence of arteriosclerosis with syphilitic disease makes it difficult to separate these two factors as causes of coronary disease. Probably less than 10 per cent of the cases with aortic syphilis are associated with coronary disease of syphilitic character. In this series, a description of the involvement of the coronary orifices in the typical wrinkling of syphilitic aortitis was found only 10 times, an incidence of 8.4 per cent.

3. Aortic insufficiency is found in about 20 per cent of the hearts associated with syphilitic aortitis. It is the lesion most easily recognized and is most likely to be present in the advanced cases. In this series, it occurred in 19, or 37.2 per cent, of the hearts weighing over 450 grams.

4. Hypertrophy of the heart is a significant index of the degree of cardiac involvement in cardiovascular syphilis. This sign is absent in the latent stage of the disease but becomes increasingly important as signs of cardiac disease appear. In a group of 44 cases in which autopsy showed definite cardiac enlargement of various degrees, up to a maximum of 50 per cent, 21 died of intercurrent disease, and 15 of these had not been diagnosed as subjects of cardiac disease. Some of these presented symptoms of acute disease so marked as to cloud the picture, but others did not. Both aortic regurgitation and hypertension were infrequent in this group. The presence of an unexplained or "idiopathic" cardiac hypertrophy in individuals of middle life may well excite the suspicion of syphilis.

5. The two important causes of cardiac hypertrophy are aortic regurgitation and hypertension, which latter is a common occurrence in this type of case. There is a significant incidence of contracted kidney with advanced stages of cardiovascular syphilis.

6. In this series, aneurysm was found more frequently in the cases characterized by relatively minor cardiac symptoms. These results seem to illustrate the frequency with which aneurysm may be present without involving the heart or causing symptoms of cardiac disease.

In conclusion, I wish to make grateful acknowledgment of my indebtedness to Dr. R. H. Jaffe, pathologist of the County Hospital, for helpful suggestions and criticism in the preparation of this paper.

DISCUSSION

Dr. J. W. McMeans, Pittsburgh, Pa.—It is my impression that many of the changes suffered by the heart in syphilis are indirectly attributable to luetic aortic

intimitis involving the coronary orifices and leading to partial or complete occlusion of these vessels.

Dr. George Herrmann, New Orleans, La.—We are interested in cases of hypertrophy in syphilitic heart disease with and without regurgitation. Dr. Carr spoke of the greater thickness of left ventricular wall as indicating preponderating hypertrophy. I would like to know whether any actual weights of the separated left and right ventricles were recorded so that the relative proportions of the left and right heart could be reported. I believe that such and only such figures are adequate. In a small series of some twenty-five syphilitic aortic regurgitation hearts I found relatively little real left ventricular preponderance.

Dr. H. E. B. Pardee, New York, N. Y.—I would like to know if you found any hypertrophied hearts which did not also have an aortic insufficiency or hypertension?

Dr. Carr (closing).—I think there were a number of cases moderately enlarged without regurgitation or hypertension. I hope to work up the data on this subject as part of a more complete study.

MICROSCOPIC PATHOLOGY OF CARDIAC SYPHILIS

CHAUNCEY C. MAHER, M.D.
CHICAGO, ILL.

IN SPITE of the fact that an immense amount of study has been devoted to the microscopy of cardiac syphilis, apparently there remains considerable dissension among observers as to that which constitutes the exact picture of this disease. May I preface the discussion of this subject by briefly stating our conception of the pathogenesis of cardiac syphilis and mention a few of the difficulties encountered in this type of study?

It is assumed that early in the second stage of a syphilitic infection a spirochetemia occurs in which the heart suffers early changes, reaching the major involvement when aortic regurgitation supervenes. The pathological picture present varies with the amount and efficacy of treatment, with the resistance developed in the individual, and probably with the malignancy of the strain. Pathological entities other than syphilis, such as hypertension, arteriosclerosis, and other chronic or acute infections, may distort the picture. Terminal death-producing phenomena merit a special mention. From another standpoint it would seem exceedingly important to mention that syphilis is particularly likely to be localized in its activity. It is for this reason that I would like to present to you the following method of selection of material to disclose adequately the true microscopic picture of cardiac syphilis. Sections to be studied were chosen from the following:

- Aorta, one inch above the valves.
- Aorta, two and one-half inches above the valves.
- Aorta, mid arch.
- Aorta, descending portion.
- One block through commissure of aortic valves.
- Six to ten blocks of the larger coronary vessels.
- Two blocks from the upper part of the septum.
- One block from midseptum.
- One block from lower septum.
- Three blocks from each of the right and left ventricular walls.
- One block from the right and left auricular muscle.
- One block from the papillary muscle.
- Blocks were also taken from any particular spot where any gross muscular pathologic change was evident.

The cases selected for study are necessarily limited, because of the previously mentioned distorting factors. Inasmuch as aortic regurgitation represents the acme of syphilitic involvement of the heart, both as to the extent and severity of the process, only this entity was chosen.

Furthermore, cases in which hypertension, renal disease, acute and chronic infections, arteriosclerosis and those in which death was a lingering process were excluded, leaving syphilis as the single lethal factor.

There are essentially three modes of attack for study of this problem. One may study the inflammatory cellular reaction, with its subsequent replacement by connective tissue, or the degenerative changes which the parenchyma undergoes, or finally, that which is probably the most difficult, staining the spirochetes *in situ*. Obviously, it is

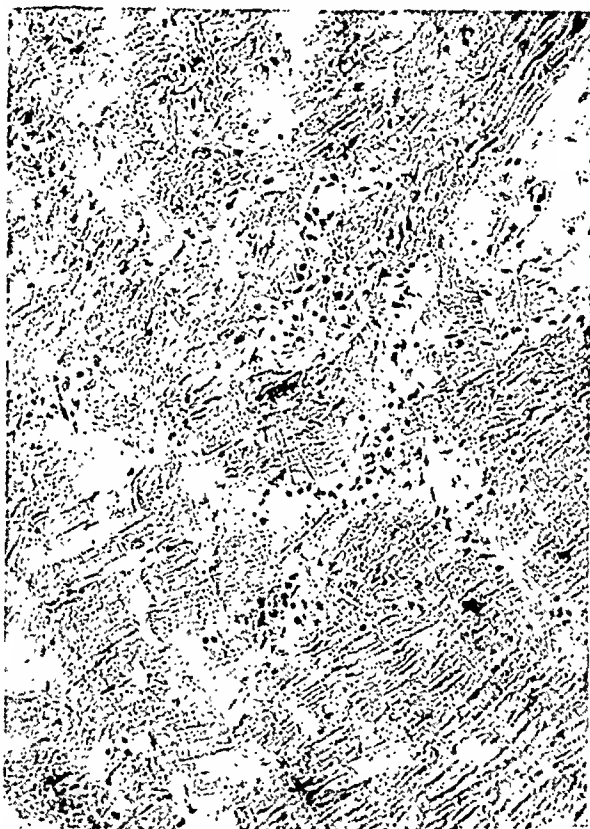


Fig. 1.

upon this latter method that the whole question revolves. A simple method for the demonstration of spirochetes, workable in all hands, is a necessity. Adaptations of the neuropathologist's staining methods for inflammatory cellular reactions will undoubtedly add much to our knowledge. The scope of this preliminary study is limited to the demonstration of the cellular infiltration, with reference to its location and extent by the ordinary hematoxylin-eosin stain.

The general pathologist and the neuropathologist have stressed the presence of lymphocytes, plasma cells, new connective tissue elements, and the endothelial proliferation in the blood-vessel intima, with new blood-vessel formation as criteria of active syphilitic involvement. The

cellular infiltration about blood vessels is generally accepted. I would like to point out the similarity of the microscopic picture of general paresis and that of aortic regurgitation, stressing the vascular phenomena, the visceral pericardial changes and the muscular infiltration.

Coronary Arteries.—The main arteries and their larger branches are the seat of a round-cell infiltration which is exactly like that seen in the aorta. In the first few centimeters of their courses this is liable to be exceedingly dense. As the arteries subdivide, the collections of cells become less frequent and smaller in size. The invasion is characteristically located in the adventitial coat but may invade the media or



Fig. 2.

the subintima. In addition to the acute process, connective tissue replacement may be seen, particularly in the media. In the larger vessels intimal proliferation with subsequent hyalinization, while apparently a part of the syphilitic process in these cases, has also been observed in other types of disease.

Visceral Pericardium.—Localized groups of lymphocytes and plasma cells were commonly encountered in the visceral pericardial membrane and beneath it. A more common finding is a more scattered infiltration of these same cells. Apparently the end-result here is the same as in any syphilitic process, i.e., connective tissue proliferation with thickening of the visceral pericardial layer. Dr. Jaffe, chief of the

pathology department of Cook County Hospital, to whom I am indebted for his efficient criticism of this work, informs me that these larger areas may be detected grossly.

Myocardium.—In the septum and in the walls of either ventricle this same infiltrative process may be seen. It was seldom found as a diffuse uniform process. Some sections were without findings; others showed localized areas of infiltration with apparently normal muscle intervening. In the interstitial tissue when a vessel is cut in cross-section, one commonly finds a scattering of lymphocytes and plasma

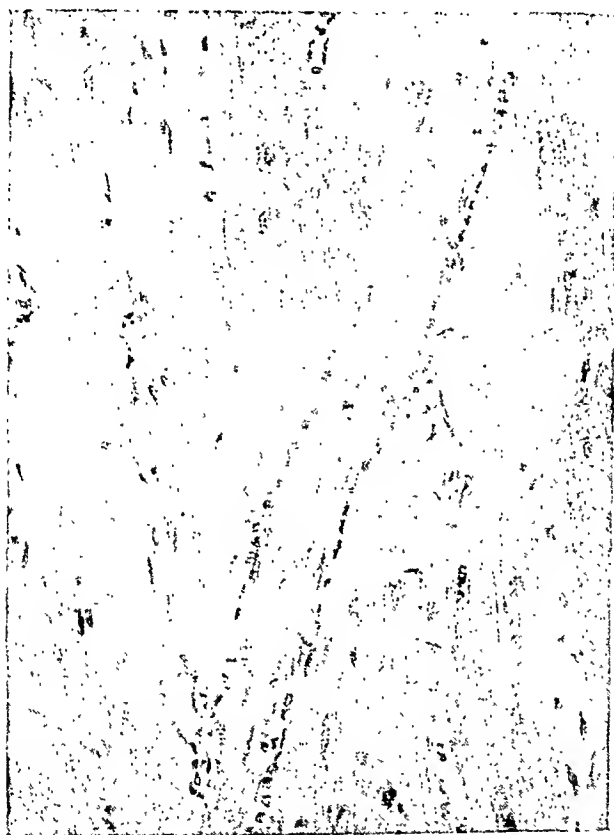


Fig. 3.

cells in the loose fibrillae. Sections showing the muscle fibers longitudinally with the interlying capillary frequently have a single layer of round cells lying about it. This single-file arrangement of cells between the muscle fibers was pointed out by Warthin some years ago. Patches of fibrosis composed of connective tissue of varying age are quite common.

Fig. 1 shows a diffuse round-cell infiltration in the muscle taken from the wall of the left ventricle. Fig. 2 shows a localized group of round cells near the epicardium extending into the muscle. Fig. 3 shows a capillary cut tangentially with the endothelial elements appearing dimly out of focus, with a single layer of round cells lying just

outside the wall. This latter is a characteristic picture but not readily demonstrable.

SUMMARY

Five cases of uncomplicated and probably untreated aortic regurgitation were studied microscopically from many sections. A method of selection of blocks of tissue for intensive study is presented. The inflammatory reaction, presumably due to syphilis, by exclusion of other factors was found to be a lymphocytic and plasma cell infiltration about the coronary arteries and their branches and beneath the visceral pericardium. In the muscular tissue the invasion appeared between the fibers and can be demonstrated about the capillary walls.

DISCUSSION

Dr. E. P. Carter, Baltimore, Md.—We have been interested in this question of differentiation of the luetic process, and we have noticed particularly these areas of diffuse, round-celled infiltration, but we have no positive proof that it is the syphilitic process. Does Dr. Maher feel that he can make a diagnosis from his findings in the absence of a history of syphilis? Another question, why does the lesser circulation seem to remain so constantly free from any syphilitic involvement?

Dr. Kurtz, Madison, Wis.—How often was this infiltration found? Was it found in 100 per cent of cases? Was there any difference noted in cases with aortic aneurysm and those with aortitis higher up?

Dr. Paullin, Atlanta, Ga.—I would like to ask if the speaker has demonstrated spirochetes in the pericardial lesions.

Dr. R. W. Scott, Cleveland, Ohio.—Had you any criteria to differentiate the myocardial lesions in coronary disease from those seen in diseased hearts from other causes?

Dr. Maher (answering Dr. Carter).—I do not think I would be able to make this diagnosis without the clinical history. I do not know why the smaller vessels remain free. In regard to aneurysm and regurgitation, we studied few aneurysms intensively, but aneurysm affects the heart itself least, regurgitation most, and aortitis lies between. I have never demonstrated spirochetes, but I think they are there. I have used Dieterle's and Warthin's stain, also Levaditi's stain. Answering Dr. Scott, the coronary artery picture is the same in syphilitic lesions as in lesions from other causes. The vessels show round-cell infiltration.

Dr. W. W. Hamburger, Chicago, Ill.—Does Dr. Maher feel that this picture of microscopic pathology should be taken as evidence of active untreated syphilis, or had these patients been treated?

Dr. Maher.—These were untreated cases. The people were not of the intelligent class, just the type that come to a dispensary clinic. In one case that received arsphenamine, there was no difference in the picture of round-cell infiltration.

THE LOCALIZATION OF THE LUETIC VIRUS IN THE AORTA

J. W. McMEANS, M.D.

PITTSBURGH, PA.

SYPHILITIC aortitis is insidious in its onset and is, as a rule, chronic and progressive. Primarily it is considered to be a granulomatous inflammation of the periarterial tissues and adventitia characterized by lymphatic and perivascular lymphocytic infiltration and endothelial-cell proliferation. The intimal endothelium of the arterioles proliferates and in many instances leads to occlusion of the vessels. In places miliary gummata are formed. From the adventitia the syphilitic granulomatous reaction progresses by contiguity to involve the other tissues of the aortic wall.

In 1927 Peek¹ reviewed the literature on syphilis of the pulmonary artery and reported one case of this disease. He remarked that the necrotic gummatous formations of the severest type may remain entirely localized to the intima of the pulmonary artery and states that this is contrary to the observations so far described in the pathological anatomy of gummatous aortitis in that, in the latter, there is a total syphilitic mesaortitis. In the same year Saphir and Cooper² described a case of acute suppurative aortitis superimposed on syphilitic aortitis. They stated that the whole intima presented an increase in connective tissue and areas of hyalinization, in some of which a few endothelial cells and plasma cells were found. In addition to these changes, large formed vessels extended up to the intima and were surrounded by lymphocytes and circumscribed areas of leucocytic infiltration. They noted that the acute suppurative aortitis was formed exclusively in the intima and inner portion of the media, which areas are supplied not by the vasa vasorum but by the circulating blood. A diplococcus lanceolatus was recovered from the blood at autopsy.

In the past several years I have had an opportunity to perform necropsies in the service of Dr. W. J. McGregor, coroner of Allegheny County, Pennsylvania, and I have been fortunate to find a large number of cases of syphilis of the aorta in its various stages.

One of the outstanding features of this disease is the capillary endothelial-cell proliferation which it is agreed constitutes a typical obliterating endarteritis. For some reason or other a peculiar chemotactic influence is exerted upon endothelial cells of lymph spaces and capillaries by the virus of syphilis. If this is true in the case of the vasa vasorum of the aorta and again in the intima of the pulmonary artery, there is no reason why endothelium in other locations should not respond to the influence of the virus. Certainly, the endothelium of the

aortic intima differs in no material way from those already mentioned, and there is some evidence to show that there is a reaction in aortic intima which is comparable to that which is considered characteristic for syphilis in the outer coats of this vessel.

That the syphilitic granulomatous reaction does not remain limited to any part of the wall of the aorta is illustrated by the findings in a case of an individual (W. B. W., Nov. 14 1929) found dead in a rooming house. No history could be obtained. Grossly the wall of the aorta was thick and tough. The intima was wrinkled and puckered. The condition involved the base of the vessel extending into the sinuses of Valsalva. The aortic leaflets were moderately shrunken. The mitral valve was healthy. The coronary orifices were pin-point in char-



Fig. 1.—Low power field showing older crevice-like lesion in intima (W. B. W.) with surrounding inflammatory reaction.

acter and surrounded by thickened pinched-in intima. The greater part of the aorta was involved with the condition extending into the lower part of the abdominal portion.

Microscopically a section of the aorta through the orifice of the left coronary artery showed a thick, pink-stained, laminated intima in the lower layers of which there were cells with large, swollen, stippled nuclei. Just beneath this region there were the outposts of lymphocytic infiltration. These cells were related to a rich nest of capillaries that were situated just beyond the first cellular layers of the intima. The larger cells were endothelial in type and situated in the perivascular lymph spaces about these vessels. Red blood cells were present in all of these vessels. The vessels were centered in a matrix of cells which had swollen, oval, round or spindle-shaped nuclei. Caught in

the interstices of this meshwork there were lymphocytes and occasional polynuclear leucocytes. Capillaries and a typical granulomatous inflammation were followed through the wall at irregular intervals from the adventitia.

A section of the left coronary artery at its origin showed a proliferation of the intimal endothelial cells in a fine papillary arrangement with the cells at right angles to the surface. Numerous leucocytes and occasional lymphocytes infiltrated the intima and extended for a short distance into the wall. There was no evidence of atherosclerosis. The reaction in the intima of the aorta and in the intima of the left coronary artery were contiguous and presented all the characters of a typical syphilitic granuloma. Such areas of intimal change are prone to



Fig. 2.—High power field of case (W. B. W.) showing endothelial cell proliferation and vascularization of deep intimal tissues. About orifice of left coronary artery.

undergo necrosis with the development of an ulcerative intimitis which may serve as a focus for the entrance of an acute mycotic invasion of the wall or of itself foster the formation of a mural thrombus. Over such areas of granulomatous change I have observed the margination of leucocytes upon the intimal endothelium and then the penetration of the leucocytes into the subjacent superficial layers, internal to the remnants of the frayed and hypertrophied internal elastic layer. In review, the cause of death in this case was coronary occlusion secondary to a luetic intimitis of the aorta.

Recently I have observed three cases of mural thrombosis of the ascending aorta complicating ulcerative luetic intimitis not associated with fatty degeneration or atheromatous change in the intima. In all of these cases the aortic and mitral valves were healthy. In the first

ease (M. W., Sept. 16, 1929) the intima of the ascending aorta was smooth and pale. As the arch was reached, the intima changed in character, becoming finely wrinkled and puckered. The intima of the branches of the arch showed a similar appearance at their orifices. Here the wall of the vessel was from two to three times as thick as in the ascending or thoracic parts. On the posterior wall there were three firmly adherent, grayish-red thrombi, one of which measured 1 cm. in diameter. The latter clot was situated just below the orifice of the innominate artery. The other two clots were pea sized.

A section of the aorta showed a marked perivascular infiltration of lymphocytes about the vasa vasorum. Associated with the lympho-

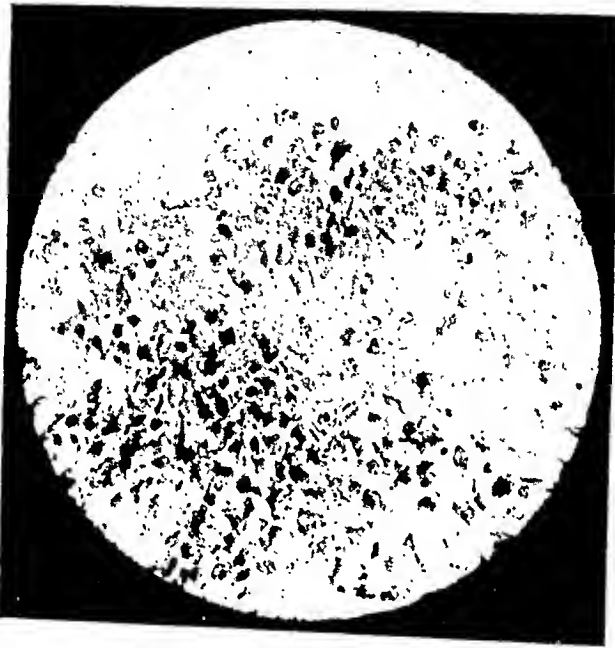


Fig. 3.—High power field from another case (H. W.) showing suggestive papillary arrangement of intimal reaction about orifice of left coronary artery.

cytes there were numerous plasma cells and some endothelial cells. These small arterioles were surrounded by thick whirls of connective tissue, and their lumina were irregular in outline. The outer coats of the small vessels were infiltrated by the inflammatory cells. In the intima overlying this reaction there was a loose vascular meshwork, the vessels of which contained red blood cells. About these vessels there was pink-stained, fibrillar tissue in which occasional elongated nuclei were seen. Lymphocytes and plasma cells together with occasional large mononuclear cells which had single large nuclei and irregularly shaped pyramidal cell bodies infiltrated the tissue. Numbers of cells were seen which showed two nuclei. This inflammatory zone led to a hillock where the thickness was entirely limited to the intimal tissues. The lower border of the elastic layer could be followed along

beneath this raised area. Over the surface of the raised area there was a single layer of flattened endothelium. Between this endothelial covering and the internal elastic layer there was a striated network of

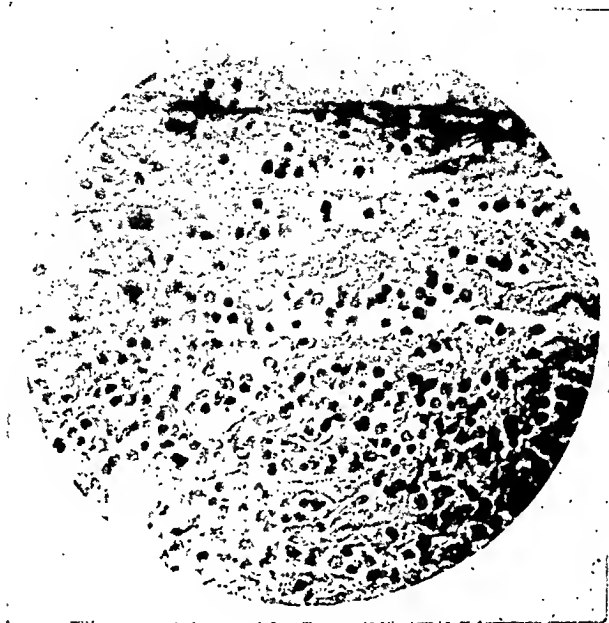


Fig. 4.—High power from field from border of intimal thrombus showing intimal reaction in case (M. W.). Note the endothelial cell proliferation with lymphocytes and plasma cell infiltration. There is debris upon the intimal surface.

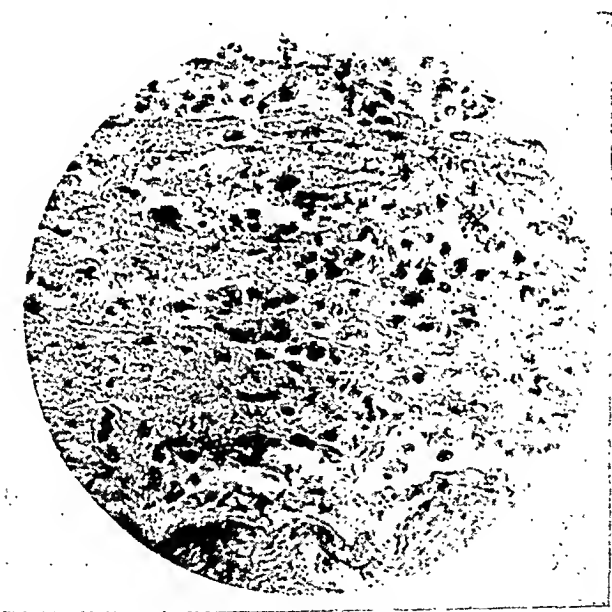


Fig. 5.—High power field of another area in intima of case (M. W.).

pink-stained, fine fibrils in which there was incorporated homogeneous, pink-stained material. There were swollen, round and oval nuclei which stained moderately blue. In other areas they were just visible,

and about them there were pink-stained areas with the suggestion of indefinitely defined cell bodies.

Beneath this area in the media approaching the zone between the middle and inner thirds there were small blood vessels with perivascular infiltration which was like that found in the adventitia. Other areas of intimal reaction were seen where the tissue between the internal elastic layer and the endothelium was packed with lymphocytes and occasional polynuclear leucocytes. The numbers of lymphocytes gave the appearance of a chronic inflammatory reaction like a granuloma. As the intimal reaction was followed the numbers of lymphocytes increased to the edge of the thrombus which has been described in the gross specimen. This thrombus was laminated. It consisted of

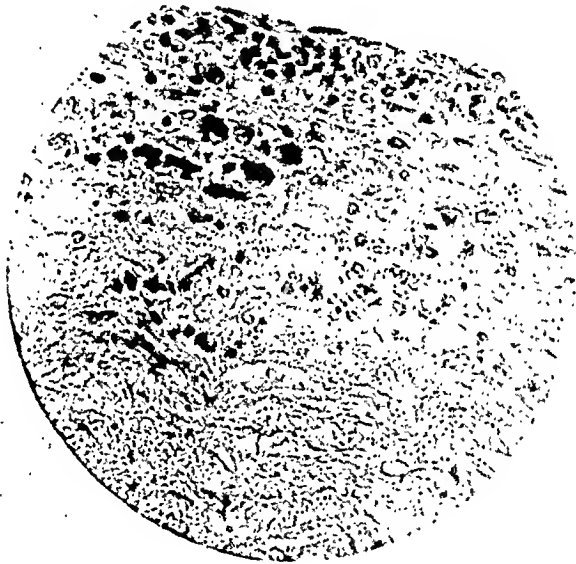


Fig. 6.—High power field showing intimal reaction in case (M. W.). Note the large multinucleated cells and endothelial proliferation.

pink-stained fibrillar material and concentrated pink-stained clumps. The character of the inflammatory reaction associated with this clot was not of an acute nature. Leucocytes were not found in it. Large numbers of swollen, round, oval and elongated spindle-shaped cells were seen invading a finely reticulated pulp. The reaction was entirely between the elastic layer and a thin zone of lymphocytes which covered the ulcerating surface. In another area the reaction dipped through the internal elastic layer. Lymphocytes and swollen mononuclear cells and fibroblasts were seen in the area. A wedge-shaped extension followed through the internal elastic layer to a small blood vessel which was almost at the inner border of the media. Below this there was a network of vessels in the media and adventitia. In another area there was a layer of blood clot, part of which was infiltrated by

leucocytes. Part of the clot was necrotic. In some places free blood still remained in the clot. Some large mononuclear cells with swollen nuclei were seen. On either side of the thrombus flattened endothelial cells were found extending over the surface. In review, the cause of death in this case was acute alcoholic gastroenteritis. The findings in the aorta were incidental, and they constituted an early but well-defined syphilitic intimitis which had undergone gummatous necrosis. The vital first part of the aortic intima was uninvolved.

In the second case (F. Z., Oct. 31, 1929) at a distance of 2 cm. above the right anterior aortic segment there was a raised, firmly attached greyish-red thrombus which measured 2.5×1.5 cm. It extended almost entirely across the anterior face of the intima. From the lower end of the thrombus a tail of red granular clot extended into the left coronary artery almost completely occluding it. This part of the thrombus was not attached, and the intima of the coronary vessel was unaltered. The heart muscle showed no evidence of infarct. The aortic and mitral cusps were thin, smooth and glistening. The right coronary orifice and the intima of the sinuses of Valsalva were unaltered. The wall of the aorta was irregular, thick and tough, and the change persisted to the level of the diaphragm. There was a fine puckering of the intima, but the greater extent of this membrane was puffy and glassy. The orifices of the vessels of the arch were irregularly dilated and surrounded by a thick wrinkled intima.

Sections of the aorta showed a marked thickening of the adventitia and an associated perivascular lymphocytic infiltration. The endothelial cells in the capillaries were hyperplastic, leading to almost complete occlusion of two of the vessels. Some large nerve bundles were seen in lymphocytic inflammatory zones, but apparently there was no infiltration of their substance. Small vessels could be followed from the adventitia into the wall of the aorta until they advanced to the inner border of the media. Associated with this vascularization there was a lymphocytic and plasma cell infiltration. The media was split and frayed by the reaction. Areas of cellular connective tissue cut through the media along the line of vascularization. Patent vessels were still present in these scars. Where the capillary tufts advanced to the subintimal tissues, the inflammatory reaction extended through to the intimal surface upon which there were pink-stained necrotic debris and a large massive thrombus of fibrin, blood, leucocytes, mononuclear cells and some eosinophiles. At one place in the intima there was a necrotic zone with numerous leucocytes, some lymphocytes and nuclear debris. Leucocytes could be traced from this area outward into the media where they were found free and in the small capillaries. In places the leucocytes formed massive collections. Beneath the thrombus fibroblasts were arranged radially to the intima, advancing into the base of the adherent thrombus. In review, this case showed

an advanced gummatous necrosis of the aortic intima resulting in a luetic intimal ulceration above the orifice of the left coronary artery. A thrombus formed upon this ulcer which extended downward into the left coronary orifice occluding it. Death resulted from coronary occlusion.

In the third case (H. G., May 19, 1930) the aortic leaflets were free, smooth and glistening. Above the junction of the right and left anterior leaflets there was a grayish-red thrombus which extended across the face of the aorta 0.5 cm. above the left anterior leaflet, passing into the left coronary orifice, practically occluding it. The thrombus was attached. It measured 1.6×1 cm. and projected on the surface a distance of 0.3 cm. The thrombus extended into the coronary orifice a distance of 0.3 cm. The intima of this vessel was not puckered or wrinkled, and it did not show any areas of atherosclerosis. The intima about the orifice was mucoid, watery and edematous, and for a distance of 2 cm. above the upper level of the leaflets there were fine furrows. The orifice of the right coronary was slit-like and not larger than a pinhead. About it there was a thick, bluish-white, mucoid nodule. There was some puckering and wrinkling of the intima of the left anterior and of the posterior sinuses of Valsalva. The intima of the aorta beyond the zone of 2 cm. above the upper border of the aortic leaflets was pale yellowish-white. In the middle of the posterior wall of the left ventricle of the heart there was an almond-sized infarct which was undergoing coagulation necrosis. In the meshes of the infarct there was a coagulated material like gelatin. This infarct was associated with a change in the finer radicles of the right coronary artery. There was also a small red infarct in the anterior surface of the upper pole of the right kidney.

A section through the thrombus showed no macroscopical evidence of atheroma or calcification in the wall. The thrombus was situated upon a bluish-white, pearly, edematous nodule in the intima which measured 0.2 cm. thick. The entire thickness of the wall through this area was 0.5 cm. When the thrombus was included, the thickness was increased to 0.75 cm.

Microscopically a section of the aorta through the clot above the left coronary artery showed a pink-stained, clumpy material in which there were scattered leucocytes, lymphocytes, swollen endothelial cells and fibroblasts. There were some small irregularly defined spaces in which there were unevenly placed swollen endothelial cells. Red blood cells were found in these spaces. The thrombus rested upon a base of leucocytes, lymphocytes and endothelial cells. From this ulcer to the level of the internal elastic layer there was a laminated, pink-stained tissue in which thin, fibrillar, deeply stained nuclei were distributed. Leucocytes extended into this tissue for some distance. As the base of the ulcer was followed toward the orifice of the coronary artery,

numerous small cleft-like spaces were developed. These spaces were lined by endothelial cells that had oval and round nuclei. Some of them were deeply stained, others were vesicular. Many of the spaces were completely filled with these cells. Lymphocytes, some leucocytes, and occasional eosinophiles were seen in the tissue.

Below this zone there was a necrotic tissue which involved the intima and the media. Nuclear debris, blue-stained, granular material and leucocytes infiltrated this area. Gram-Weigert sections were negative for microorganisms. The leucocytic infiltration could be traced through to the midportion of the media where irregular areas of this layer were necrotic and infiltrated by leucocytes. The necrosis of the media stopped at the level of the large vasa vasorum. Numbers of

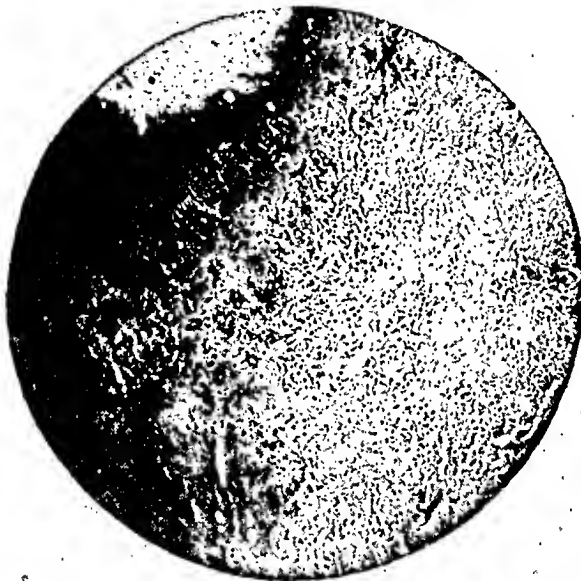


Fig. 7.—Low power field of case (H. W.) showing intimal reaction about orifice of left coronary artery.

large cells with irregularly shaped, bilobed granular nuclei were found in the region of these vessels. Leucocytes were present in this granulomatous area. They could be followed from the intima through the media to it. In the outer part of the media there was endothelial cell proliferation in the vasa vasorum and perivascular spaces with numbers of lymphocytes, some plasma cells but no leucocytes. There was no evidence of atherosclerosis.

At the border of the thrombus the intima was puffy and meshy in character. It had the microscopic appearance of what might represent the mucoid, bluish-white, intimal thickening noted macroscopically. The surface endothelial cells were swollen and hyperplastic. Beneath this layer there was a zone of 10 to 12 cells irregularly arranged in a loose reticulated tissue. These cells consisted of swollen, spindle-

shaped fibroblasts, with pale stippled nuclei, deeply stained round cells and some plasma cells and an occasional leucocyte. Here and there a small space was lined by hyperplastic endothelial cells with pale vesicular nuclei. This proliferation of cells continued down to the inner border of the media. In this section it appeared that the intimal reaction was independent of that found in the media in other places, as the media in these sections was free. In review, this case showed a gummatous necrosis of the aortic intima resulting in a luetic intimal ulceration upon which a thrombus formed. The thrombus extended down into the left coronary orifice occluding the vessel. Death resulted from coronary occlusion.

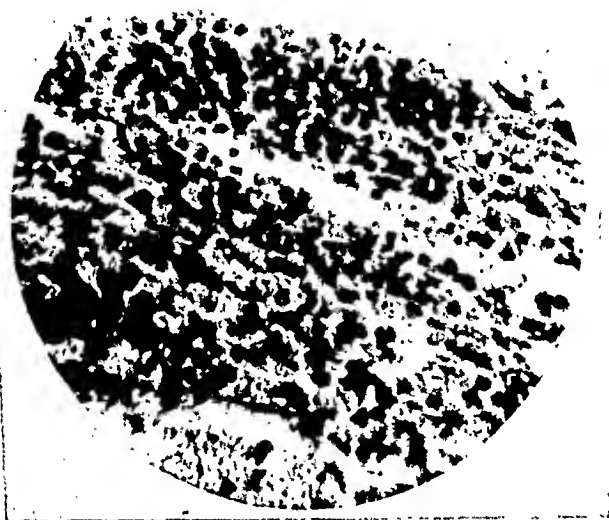


Fig. 8.—High power field showing a dense inflammatory intimal reaction (H.E.).

In these cases the zones below the thrombi on the intimal surface were packed with lymphocytes and leucocytes. Endothelial and fibroblastic hyperplasia was associated with small capillaries in the base of the thrombi. In the first case at the border of the thrombus endothelial cells were found extending up over the surface of it. These findings are indicative of advanced healing in this thrombus, and from this there is reason to believe that certain areas of intimal sclerosis may be healed thrombi rather than productive sclerosis secondary to deep intimal and inner medial change. If such is the case, we must remember the idea of Rokitsky³ concerning intimal sclerosis, and yet the findings in these cases are not at variance with the views expressed by Virehow.⁴

All of these cases show massive destruction of areas in the aortic wall proceeding outward through the wall from areas of ulcerative luetic intimitis. Under conditions of ulceration like those observed in

these cases it is not at all improbable that extensive destruction of the wall of the aorta and even rupture of an aneurysm may be accounted for by the extension of a progressive gummatous inflammation from the intima of the vessel through the wall.

The manner in which the intimal ulceration occurs is problematical. In certain areas hyperplastic surface cells show granular cytoplasm with poorly stained nuclei and blurred cell outlines. In these places the zones between the intimal endothelium and internal elastic lamella are crowded with inflammatory cells. This would naturally lead to ulceration at the point of least resistance, which is upon the intima. When this occurs a raw surface, so to speak, is produced, upon which the elements of the blood may gravitate with resultant thrombus for-

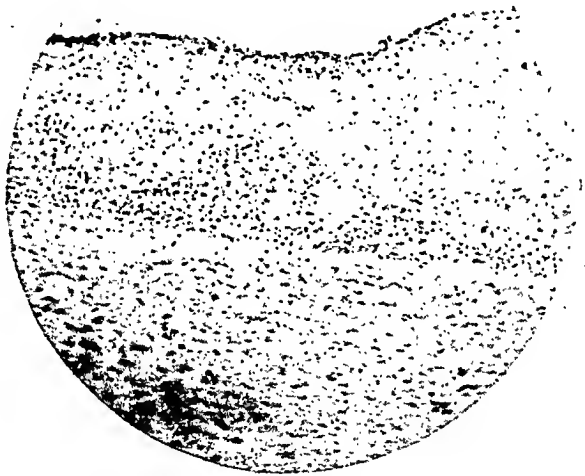


Fig. 9.—Low power field showing thickening of intima with inflammatory infiltration (H.g.) Media is free.

mation. Some years ago I called attention to the intimitis which occurs in the vessels of the brain in meningitis and suggested that such a condition may precede thrombus formation.

Although blood cultures were not made in these cases, the possibility of mycotic invasion of the wall through areas of intimal ulceration cannot be discounted. Aside from the bacteriological findings the cases included in this report are not unlike the case reported by Saphir and Cooper. However, the findings in these cases suggest that the granulomatous intimal change precedes the advent of the acute inflammatory invasion of the intima. A gummatous necrotic area in the intima would form a favorable nidus for the localization of organisms circulating in the blood. However, the reactions observed in the aortic intima of these cases would indicate that gummatous necrosis is of

itself sufficient to be responsible for the entire changes noted. The attraction of leucocytes to such areas does not necessarily imply mycotic invasion. It is only necessary to mention the leucocytic infiltrations seen in the media of the aorta in gummatous necrosis of this layer and those leucocytes found in and about areas of infarcted heart muscle. The leucocytes respond to chemotactic influence of the necrotic process even in the very early stages of gummatous necrosis. This is clearly shown in the first case where margination of leucocytes upon an area of unbroken luetic intimitis had occurred. Furthermore, leucocytes could be traced for some distance into the underlying tissues. Although the secondary leucocytic reaction in this case was mild, it is possible that it represented the prestage of the more severe reactions described in the last three cases.

Although it is impossible definitely to indicate the final results in these cases, it would appear that there is some evidence to support the contention that nodular thickenings of the intima noted in syphilitic aortitis are not entirely due to secondary reactive fibrosis subsequent to medial damage. When the process is not too severe, rapid and extensive, the intima may recover and heal. We have seen that the inflammatory process in the intima is accompanied by progressive as well as by secondary acute degenerative changes.

Fibroblasts and endothelial cells were found proliferating in the intima associated with small capillaries, lymphocytes and leucocytes. Under ordinary circumstances in the end, even when ulceration occurs, the fibroblastic proliferation would bring about the repair of the injured layer, leaving the intima thickened, puckered and hyaline in appearance. I have noted intimal puckering microscopically in zones of luetic intimitis where the underlying media was entirely free from inflammation or scarring. When ulceration occurs, thrombus formation is stimulated. Organization of such thrombi increases the probability of intimal hyalinization. However, with the advent of ulceration, thrombus formation and possibly mycotic invasion of the area, extensive destruction of the wall may follow. I have seen crypt-like ulceration in the wall of the aorta with destruction of the intima and media and red blood cells infiltrating the last few strands of the adventitia.

Virehow demonstrated that the intima, like other nonvascular structures, may be the seat of inflammation, and that a proliferation of its own cells leads to the nodular masses on the surface. In syphilis we are dealing with an inflammatory process of long duration, and the nodular thickenings which occur in the aortic intima may be comparable to certain other inflammatory reactions of the intima which are always accompanied by a connective tissue disturbance of a proliferative kind. If this were not true in part, at least, it would be difficult

to account for the changes noted in the nodular thickenings about the coronary arteries in two of these cases. Furthermore, when one considers the endarteritic process observed in the vasa vasorum of syphilitic aortitis, it is difficult to understand why this same granulomatous process cannot involve the intima of the aorta with the end-result in both instances the same, hyalinization of the injured tissue.

Mesaortitis has been considered in the past the important lesion of syphilis of the aorta. First, because it was so obvious microscopically, and second, aneurysm, a very important end-result of aortitis, was supposed to occur after destruction of the media. This idea held despite the fact that aortic regurgitation associated with a syphilitic aortitis represents the most serious end-result of syphilis on the cardiovascular system. This lesion can only be produced by involvement of the aortic intima. The media does not come into this picture at all. Furthermore, the closure of the coronary orifices, also a lesion of great importance, is purely an intimal manifestation of lues. Therefore, as Warthin has suggested, the term syphilitic aortitis is much to be preferred to syphilitic mesaortitis, both from clinical and pathological grounds. Our purpose is to indicate four cases in which there was luetic intimitis associated with the changes commonly recognized in the adventitia and media.

In the cases under discussion, as indicated by the photomicrographs, it is obvious that there is a syphilitic inflammatory intimal lesion. Intimal lesions due to syphilis are well recognized in small vessels under the term endarteritis proliferans. Further, they are known to occur in the intima of the pulmonary artery and Winternitz⁶ has stated that in congenital lues there is marked involvement of the intima with spirochetes predominating in this layer. By analogy there is abundant proof that luetic intimal disease is not a peculiar condition and occurs far more frequently than is generally believed. The intima of vessels is prone to show acute inflammatory reactions in other infections. Some years ago I demonstrated the acute intimal lesions noted in the cerebral vessels in acute meningitis due to a variety of microorganisms and also showed that these small arteries were invaded simultaneously by inflammatory cells from the intima and adventitia.

If these facts are true, what proof is there to show that an acute luetic lesion of the aortic intima does not occur? From the reactions observed in the cases under discussion, there is ample ground to believe that intimal luetic aortitis does occur and further that the aorta is simultaneously invaded from the intima and adventitia. The media is secondarily involved from both of these coats and suffers in extent depending upon the severity of the process in the intima on the one hand and the adventitia on the other.

CONCLUSIONS

It is our belief that in syphilitic aortitis the intima is involved primarily by direct infection from the blood stream. It may also be involved from the adventitia through the vasa vasorum. Histologically, the lesions are the same.

Undoubtedly, the most serious lesions produced by syphilis on the aorta and heart are the syphilitic aortic endocarditis with regurgitation and occlusion of the coronary orifices. This is intimal disease. Therefore, it would appear that luetic intimal disease of the aorta is more important clinically than is medial disease.

REFERENCES

1. Peck, Samuel M.: Pathologic Anatomy of Syphilis of the Pulmonary Artery, Arch. Path., 4: 365, 1927.
2. Saphir, Otto, and Cooper, George W.: Acute Suppurative Aortitis Superimposed on Syphilitic Aortitis, Arch. Path., 4: 543, 1927.
3. Rokitsansky: Handbuch der speciellen path. Anat., 1844, p. 524. Cited by author in paper on Occurrence of Arteritis in Meningitis.
4. McMeans, J. W.: Occurrence of Arteritis in Meningitis, Am. J. M. Sc., 151: 249, 1916.
5. Winternitz, M. C.: The Pathology of Syphilitic Aortitis With a Contribution to the Formation of Aneurysms, Johns Hopkins Hosp. Bull., 24: 212, 1913.
6. Virchow: Virchow's Arch., 77: 380, 1879. Cited by author in paper on Occurrence of Arteritis in Meningitis.

OBSERVATIONS ON 107 CASES OF SYPHILITIC AORTIC
INSUFFICIENCY, WITH SPECIAL REFERENCE TO THE
AORTIC VALVE AREA, THE MYOCARDIUM,
AND BRANCHES OF THE AORTA

O. SAPHIR, M.D., AND R. W. SCOTT, M.D.
CLEVELAND, OHIO*

THIS paper presents in summary form the salient pathological features observed in 107 cases of syphilitic aortitis with involvement of the aortic valve area. A more detailed report of this work will be published shortly.

Gross Changes in the Aorta.—Characteristic gross syphilitic lesions were found at the aortic root, including the first 4 cm. of the vessel in all cases. These changes extended upward as far as the arch of the aorta in all but two instances. Gross syphilitic lesions in the descending aorta occurred in 20 cases. In 91 instances the descending aorta showed changes due to arteriosclerosis. In 26 cases a definite dilatation of the aortic ring was noted. Aneurysmal dilatation of the aorta was found in 16 instances, 3 in the first segment involving the sinns of Valsalva, 7 in the ascending arch, and 3 in the descending aorta. In two cases both the first segment and the ascending arch were involved, and in one both the ascending and descending aorta.

Histological Changes in the Aorta.—In addition to the well-known medial changes of syphilitic aortitis, we were impressed, particularly in early cases showing minimal gross lesions, by the frequency of involvement of the vasa vasorum in the adventitia. The vessel wall was thickened with more or less obliteration of the lumen. In early cases showing a lesion of the adventitial vessels, changes in the media were minimal and often difficult to demonstrate. This obliterative arteritis of the vasa vasorum of the adventitia with perivascular infiltration of lymphocytes was the most characteristic finding in both early and late cases.

Changes in the Aortic Valve.—All cases showed some grade of deformity in the architecture of the valve cusps. The commonest finding was a widening of the commissure. In 82 instances the commissures were the seat of hyaline plaques. The central portion of the free margins of the cusps was thickened in 82 cases, everted or rolled in 20, and retracted in 8.

Histological Changes.—Characteristic syphilitic lesions were found in all cases in sections from the region of the commissures and adjacent

*From the Departments of Pathology and Medicine of the Cleveland City Hospital and Western Reserve Medical School, Cleveland.

portions of the cusps. The new formation of smaller sized vessels extended from the aortic intima through the commissures to the lateral portions of the cusps in early cases. In older lesions the degenerative changes were less pronounced and those of chronic inflammation more evident. The central portions of the valve leaflet showed fibrosis and hyalinization, very few cellular elements and no blood vessels.

Coronary Arteries.—Thirty-seven cases, or 33 per cent, in this series showed some constriction of the mouths of the coronary arteries. In 8 the right coronary was narrowed; in 7 the left, and in 17 the mouths of both vessels were involved. Four cases showed complete obliteration of the left coronary, and one complete obliteration of the right. In four instances the coronary openings were definitely displaced. The histological changes at the coronary openings were similar to those observed in the aorta. The main stem and branches of the two coronaries were often the seat of simple arteriosclerosis, but in no instance were syphilitic lesions demonstrated in the coronary arteries themselves.

Other Large Arteries.—The innominate, carotid, superior and inferior mesenteric, iliac and femoral arteries were studied in 65 cases. Varying grades of arteriosclerotic changes were seen but no clean-cut gross lesions of syphilis were noted. Histologically, however, typical microscopic lesions of syphilis were observed as follows: Innominate artery in 38, carotid in 27, superior mesenteric in 12, inferior mesenteric in 3, common iliac in 11, and femoral artery in 7. In 44 cases the subclavian artery showed syphilitic changes microscopically in 19 instances.

Myocardium.—In 94 cases the heart weighed more than 400 grams. The heaviest heart in our series weighed 1050 grams. The average heart weight for the whole group of 107 cases was 600 grams. Frequently the cut section of the myocardium showed nothing unusual. In other hearts showing coronary arteriosclerosis the myocardium was the seat of fibrosis. In no instance did we find either gross or histological evidence to warrant the diagnosis of syphilitic involvement of the myocardium. The changes as noted differed in no way from those occurring in hearts hypertrophic from other causes, or in hearts the seat of coronary arteriosclerosis. Many sections were examined according to the Warthin-Starry method and also the Levaditi method, but in no instance was the spirocheta pallida found.

CONCLUSIONS

1. The primary and earliest lesion in syphilis of the aorta and larger arteries is an obliterative endarteritis of the vasa vasorum of the adventitia, with perivascular infiltration of lymphocytes. The medial changes appear to be secondary and attributable to nutritional disturbances.
2. The frequency with which syphilis attacks the root of the aorta is due to the rich supply of vasa vasorum in this region.

3. Syphilis spreads from the aorta to the aortic valves by way of small vessels at the commissure. The degenerative changes and later chronic inflammatory changes lead to fusion of the lateral margins of the leaflets with the adjacent aortic intima, producing a widening of the commissure; the most constant and characteristic gross lesion of syphilis of the leaflets. In no case have we seen a gross distortion of the aortic leaflet without involvement of the commissure.

4. Syphilis at the root of the aorta frequently involves the coronary openings, one out of three cases in this series showed varying degrees of occlusion, but no evidence of syphilis was found in the coronary vessels beyond the mouths.

5. Syphilitic involvement of large arteries—carotid, subclavian, innominate, mesenteries, iliac, and femoral arteries, is often found associated with syphilitic aortitis.

6. Invasion of the myocardium by syphilis is rare. The myocardial changes observed in this series of cases differed in no way from those seen in coronary arteriosclerosis and in hypertrophied hearts from other causes.

THE ROENTGENOLOGICAL DIAGNOSIS OF SYPHILITIC AORTITIS—A REVIEW OF FORTY PROVED CASES*

DAVID STEEL, M.D.
CLEVELAND, OHIO

THE data for this paper are taken from a study of forty cases of luetic aortitis observed roentgenologically and proved by autopsy. No case of aneurysm is included. The roentgen method varied somewhat but included in every case a fluoroscopic examination and tele-roentgenograms taken for the most part in the postero-anterior position and in many cases also in both oblique positions.

It is needless to point out that the course of the aorta should be thoroughly understood in the various positions. The diagrams (Figs. 1, 2, 3) bring out the so-called normal silhouette in the average case, but there are in addition normal factors which play an important part in this configuration. These are concerned mainly with increased and decreased spacial relations of the thoracic cage. With a high position of the diaphragm (expiration, ascites, abdominal tumors, etc.) the cage is small and the aorta is spread, appearing more prominent to the right and left and increasing slightly in height. With low position of the diaphragm the vascular shadow is narrow, and bulging to the right or left is minimal. With foreshortening of the thoracic cage, as in caries of the spine, spreading again takes place. With advancing age the aorta elongates and in accommodating itself to spacial relations becomes spiral with an increase in its height.

In addition, the silhouette is not always sharply defined, anatomical relations are many times obscure, and the superior vena cava might add to, and the brilliant trachea subtract from, the apparent silhouette, especially in the first oblique view. Even with special care it is difficult to obtain plates in an exact postero-anterior view. These factors, combined with the spacial relations of the thorax, must all be evaluated as closely as possible. We therefore often have several factors present, the value of which is almost impossible to estimate and hence various proposed measurements have a decided limitation and can often lead to error. Nevertheless, if these limitations are recognized, measurements have a clinical value. Of the various methods, perhaps the simplest and most ingenious is that proposed by Krenz-fuchs; namely, measurement of the aortic width after barium visualization of the aortic bed of the esophagus. This method has been accurate at autopsy in the few cases I have proved. Unfortunately, the

*From the Roentgenological and Pathological Departments of the Cleveland City Hospital.

method measures the aorta near the isthmus rather than near the root where syphilis is more common and more important physiologically. Just as proficiency grows with experience in other fields of medicine,

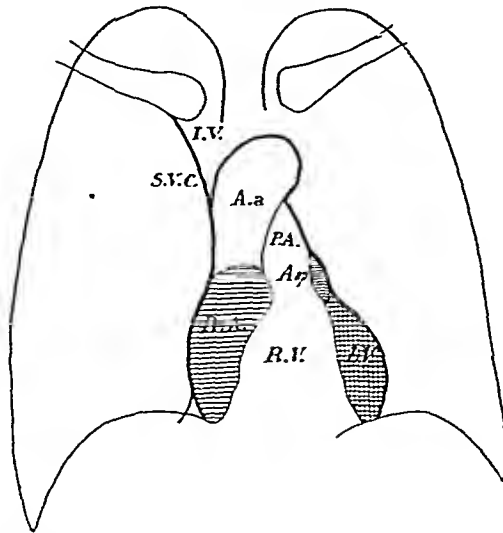


Fig. 1.—Diagram of the normal heart in the anteroposterior position. S.V.C., Superior vena cava; I.V., innominate vein; A.a., ascending aorta; P.A., pulmonary artery; A.ap., left auricular appendage; R.V., right ventricle; R.A., right atrium; L.V., left ventricle.

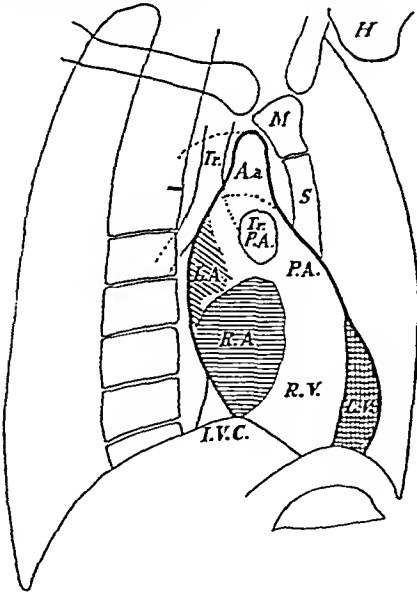


Fig. 2.

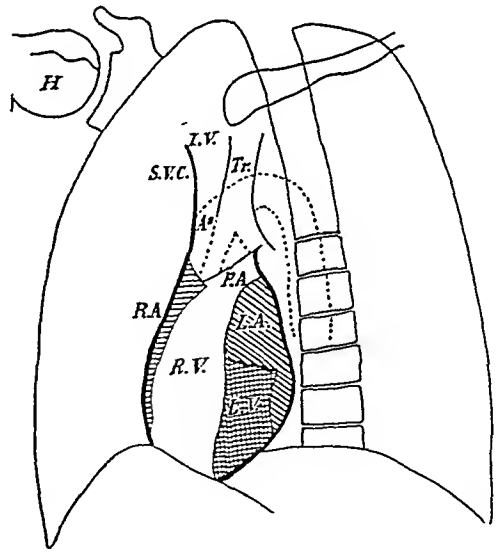


Fig. 3.

Fig. 2.—Diagram of the normal heart in the first oblique position. I.V.C., Inferior vena cava; L.A., left atrium; Tr., trachea; A.a., ascending aorta; Tr. P.A., cross-section of the pulmonary artery; P.A., pulmonary artery; R.V., right ventricle; L.V., left ventricle; M, manubrium; S, sternum; H, head of humerus.

Fig. 3.—Diagram of the normal heart in an exaggerated second oblique position. R.A., Right atrium; S.V.C., superior vena cava; I.V., innominate vein; A.a., ascending aorta; P.A., pulmonary artery; L.V., left ventricle; Tr., trachea; H, humerus; R.V., right ventricle.

so does ability to judge aortic width fluoroscopically increase after many examinations in the normal and pathological. For this reason it seems logical to depend upon experience and general impression

after fluoroscopy rather than on a number of figures subject to many unknown factors.

The differential diagnosis of the pathological aorta is one of the important problems awaiting a possible roentgenological solution. We have to differentiate, therefore, between the dilatation of atherosclerosis, advancing age, hypertension, aortic insufficiency and stenosis of the isthmus. I have had no experience with isthmus stenosis. A review of these syphilitic cases gives the definite impression that these lesions cannot always be safely differentiated roentgenologically. Yet a diagnosis can be safely made when the lesion is well marked, and this margin of safety increases notably when the clinical facts are used. Therefore, the roentgen diagnosis should always be accepted by the clinician with this condition—"provided the history and physical findings agree or at least do not oppose."

Of the forty cases there are three considered as early. These will be discussed as a separate group. The remaining cases showed changes which we all associate with a pathological aorta, namely:

1. A dense shadow often with hazy borders.
2. A high, dense and prominent aortic knob.
3. Irregular and also general dilatation.
4. Increased pulsation.
5. Association with aortic insufficiency.

In many of the cases the shadow was unusually dense, supporting previous reports that the luetic aorta produces a denser shadow than other lesions. This density is due for the most part to the increased diameter of the blood column incident to dilatation, and probably also in part to the changes in the wall. The changes in the height of the knob are most likely secondary to the changed spacial relations due to aortic elongation and dilatation. The most important sign is irregular dilatation. This presents itself as one or more localized spindle-shaped areas, not aneurysmal in dimension and involving most commonly the root. In the postero-anterior view, such a change appears as a dense shadow of the upper right cardiac arch (Fig. 4). Its border if extended would not conform to remaining portions of the silhouette. In the first oblique the anterior and posterior borders of the ascending aorta do not run parallel as normally, but, because of the greater dilatation of the root, they converge toward the aortic knob. Hence the silhouette is triangular with the base down. If the localized dilatation is near the knob, then the walls converge toward the heart and the silhouette becomes club-shaped. In the second oblique view, because the course of the aorta is now at right angles to the path of the rays, making the entire silhouette visible especially in the pathological case, local dilatations can easily be made out (Fig. 5). These local dilatations are to be expected, and they are easily explained by the disruption of the elastic fibers so common in syphilitic

aortitis. With the dilatation there is a localized increase in pulsation which should always be looked for and used as an index to dilatation.

In the later stages dilatation may become diffuse (Fig. 6). This can become extreme, and since marked dilatation is seldom seen in



Fig. 4.—Localized dilatation of the ascending aorta as seen in the postero-anterior view.



Fig. 5.—Localized dilatation of the ascending portion. The arc of this portion when continued (----) does not conform to the remaining portions of the arch (arrows).

other lesions, it has considerable diagnostic importance. The pulsations are decreased in amplitude, probably due to cicatricial changes. Increasing dilatation on repeated observation tends to rule out atherosclerosis in favor of syphilitic aortitis.

To summarize the well-marked cases of syphilitic aortitis, it can be said that the findings of a high, dense and prominent knob, a slight haziness in outline, a cardiac silhouette consistent with aortic insufficiency—



Fig. 6.

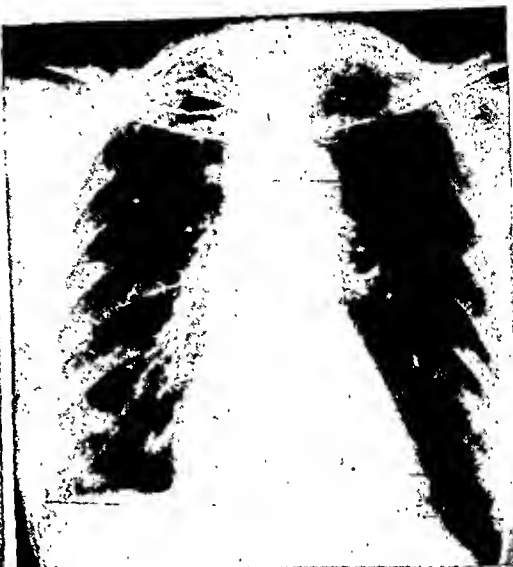


Fig. 7.

Fig. 6.—Diffuse dilatation of the aorta with aortic insufficiency.

Fig. 7.—Early case. Aortic insufficiency. Autopsy seven days after this examination.



Fig. 8.



Fig. 9.

Fig. 8.—Early case. Fluoroscopically the ascending portion of the aorta was locally dilated and showed increased pulsations. See next figure for follow-up examination.

Fig. 9.—The same case showing diffuse dilatation of the aorta and cardiac decompensation.

ciency, generalized dilatation, unless excessive, and increase in amplitude of pulsation are not in themselves pathognomonic signs for the

roentgenological diagnosis of syphilis. A marked degree of generalized dilatation is more common in syphilis and can be taken as presumptive evidence, especially if the heart shadow is small or if it occurs in a person under forty. When the various segments are variably dilated the diagnosis is almost certain. I say "almost" because Vaguez and Bordet report local dilatation of the aortic root in Hodgkin's disease. Rheumatic dilatation has been reported also. The roentgen findings should always be correlated with the clinical and laboratory findings. However, too great reliance must not be placed on the Wassermann test, because in this series of thirty-six cases so examined, fourteen, or about 39 per cent, were negative and four, or 11 per cent, were reported as anticomplementary.

The three cases referred to above represent the earliest lesions of the series and are characterized by minimal or questionable roentgenological changes in spite of the fact that at autopsy the lesion was well marked. Each case shows an increase in the height of the knob and an increased density, changes which *per se* are found in the other common lesions. When these are present alone, which is true of two of these three, the diagnosis of syphilis is not possible. However, in each case, the right upper cardiac arch has a hazy outline and shows an indefinite or questionable bulge to the right. In one case there was present in the second oblique position a slight localized dilatation with increased pulsation in the ascending aorta (Fig. 7). The significance of the hazy outline and the very questionable bulging of the right upper arch in the postero-anterior view is questionable, but seeing such a change should call for very careful fluoroscopic observation in the second oblique view for localized dilatation and pulsation. When these findings are demonstrable, the diagnosis rests upon a firm foundation. Fig. 4 represents a well-marked localized dilatation of the ascending aorta in the postero-anterior view, and Fig. 5 represents similar changes in the second oblique position. If the arc of the dilated portion is schematically continued, it will be noticed that it does not conform to the remaining outline of the arch. We must conclude, therefore, that early syphilitic aortitis is not always demonstrable roentgenologically and that its earliest sign is localized dilatation associated with a localized increase in the amplitude of the pulsations (Figs. 8 and 9).

SUMMARY

There are cases of syphilitic aortitis which present definite roentgenological changes and which are indistinguishable from the other common lesions of the aorta. The lesions can be suspected when (1) a diffuse dilatation is present and is associated with a normal sized heart silhouette, (2) a dense, high aorta is present in a young individual without a previous hypertension. It can be safely diagnosed when

localized dilatation associated with localized increased pulsation is demonstrable.

REFERENCES

1. Assmann, Herbert: Die klinische Roentgendiagnostik der inneren Erkrankungen, ed. 3, Leipzig, Vogel, 1924.
2. Eisler, F., and Kreuzfuchs, S.: Die Roentgendiagnose der Aortensyphilis, Deutsche med. Wchnschr. 39: 2145, 1913.
3. Groedel, Franz M.: Lehrbuch der Röntgendiagnostik, München. J. F. Lehmann, 1924.
4. Holmes, G. W., and Ruggles, H. E.: Roentgen Interpretation, ed. 3, Philadelphia, Lea & Febiger, 1926.
5. Holzknecht, G.: Zum radiographischen Verhalten pathologischer Processe der Brustorta, Wien. klin. Wchnschr. 13: 573, 1900.
6. Holzknecht, G.: Das radiographische Verhalten der normalen Brustorta, Wien. klin. Wchnschr. 13: 225, 1900.
7. Karsner, R. G., and Kennicott, R. H.: A Practical Method of Roentgen Examination of Heart Based Upon a Study of 100 Consecutive Normal and Abnormal Cases, Am. J. Roentgenol. 9: 305, 1922.
8. Karsner, H. T.: Human Pathology, ed. 2, Philadelphia, Lippincott, 1929.
9. Köhler, Alban: Roentgenology, Translation from Fifth German Edition, New York, Wm. Wood, 1928.
10. Kreuzfuchs, S.: Ueber eine neue Methode der Aortenmessung, Med. Klin. 16: 36, 1920.
11. Lippmann, A., and Quiring, W.: Die Röntgenuntersuchung der Aortenerkrankungen mit spezieller Berücksichtigung der Aortenlues, Fortschr. a. d. Geb. d. Röntgenstrahlen 19: 253, 1912.
12. Vaquez, H., and Bordet, E.: Radiologie du coeur et des vaisseaux de la base, ed. 4, Paris, Ballière, 1928.
13. Zehbe: Beobachtungen am Herzen und der Aorta, Deutsche med. Wchnschr. 42: 315, 1916.

DISCUSSION

Dr. Lee, Washington, D. C.—Dr. Steel referred to the size of the heart. Does he use the measurements of Bordet and Vaquez, and in what phase of respiration does he take the pictures?

Dr. Lewis A. Conner, New York, N. Y.—I do not feel that I can let this opportunity pass without adding a warning concerning the roentgenological diagnosis of syphilitic aortic disease. I think Dr. Steel has been very conservative in his statements. It seems to me, however, that it would be a pity for us to go away with the idea that this is a safe method of establishing a diagnosis. I have frequently seen the grossest sort of mistakes made because of too great reliance upon the roentgenographie and fluoroscopic appearances of the aorta. I do not think one is often justified in making that diagnosis on the basis of the roentgenological findings alone, and I am sure Dr. Steel does not think so. This is no criticism of his statements. Elongation of the aorta begins very early and is very frequent in the early fifties even without any outstanding hypertension, and doubtless there are also variations in the curves of the right and left side of the heart, but most of us are not skilled enough to use these slight signs as important factors in the diagnosis. I still believe, as I have for many years, that clinical diagnosis of syphilitic aortitis, in the absence of aneurysm and other gross deformities of the aorta, cannot safely be established before the advent of aortic insufficiency.

Dr. W. S. Thayer, Baltimore, Md.—One word in connection with Dr. Conner's remarks. The only way we can establish a diagnosis is by finding out all that we can from every source, and then by putting our heads together. The man who is attempting to make a definite diagnosis on the basis of one single method of examination, is doing a very rash thing. I think this method is an admirable one, but I would like to say more than Dr. Conner, and that is that we clinicians should

consult with our consultants, whether laboratory men or roentgenologists, and get information from every source. We cannot make a diagnosis on only one finding.

Dr. W. W. Hamburger, Chicago, Ill.—Does filling the esophagus with a heavy barium mixture add materially to the x-ray diagnosis of syphilitic aortitis?

Dr. Steel (closing).—I think the essence of the paper has been well understood. Conservatism is the keynote and hence the diagnosis of syphilitic aortitis by the roentgenologist alone should always be accepted by the clinician with the proviso “provided the history and clinical findings agree or at least do not oppose.” Plates are taken in mid-inspiration.

62191

FLUOROSCOPIC STUDIES OF THE HEART AND AORTA IN ACQUIRED AND CONGENITAL SYPHILIS

CHESTER M. KURTZ, M.D., AND J. A. E. EYSTER, M.D.
MADISON, WIS.

THE present study was undertaken for the purpose of determining, by means of physical and fluoroscopic examination, the presence and degree of cardiovascular involvement in the various types and stages of syphilitic disease. It is rather generally believed and taught that there are several strains of spirochetes each one of which is more or less selective, and that the system attacked, whether it be cardiovascular, central nervous or skeletal, depends upon the type of invading organism. With this in mind, special attention was given to a group of patients suffering primarily from syphilis of the central nervous system, and the cardiovascular findings of this group will be treated separately.

FLUOROSCOPIC APPEARANCE OF THE AORTA

In the normal individual below the age of fifty years, the ascending aorta can be visualized in all views and, in the frontal plane, can be seen lying directly behind and projecting somewhat to the left of the sternum, extending from the level of the first rib to about the third rib. The right border of the shadow cast by the great vessels is ordinarily composed of the venae cavae and shows no definite pulsation. The descending aorta normally cannot be visualized. As the age of fifty years is approached, however, certain changes begin to take place. The aorta loses some of its elasticity, becomes slightly elongated, and increases in density. As a result, the fluoroscope reveals some sagging of the ascending aorta to the right with pulsation visible to the right of the sternum, and there is a sufficient increase in density to enable the observer to visualize the descending aorta in the lateral and oblique views, and in many cases in the frontal view as well. Above the age of fifty years these changes increase progressively, and the degree of tortuosity and density depends upon the extent of the degenerative changes which are taking place.

If these changes can be demonstrated in a person below the age of fifty years, say in the thirties or early forties, it can be assumed in the great majority of cases, at least, that an infectious process of some kind has attacked the aorta producing a certain degree of aortitis. In patients more than fifty years old, one has to use a certain amount of judgment in deciding whether the changes are in excess of what might be expected at that age.

In cases where the aortitis has progressed to such an extent that aneurysm formation has occurred, a localized area of saccululation can be visualized under the fluoroscope and the diagnosis definitely confirmed.

In the present study the diagnosis of the presence of aortitis, and the degree (slight, moderate, or marked) were based upon the points above mentioned: the shape of the ascending aorta, the presence of pulsation to the right of the sternum, and the density of the descending aorta. A diagnosis of aneurysm was made whenever a localized area of saccululation could be visualized in any portion of the aorta.

CASES STUDIED IN THE PRESENT SERIES

The series is composed of 54 cases of acquired syphilis and 12 cases of congenital syphilis seen at the Wisconsin General Hospital, including both ward patients and outpatients. Of the 54 cases of acquired syphilis, 40 were males and 14 females. The ages ranged from eighteen to seventy-four years with an average of forty-seven years. Four of the females and 11 of the males denied all knowledge of any syphilitic infection, making it impossible to determine the duration of the disease in 27.8 per cent of the cases. In the remaining cases, the duration of the infection ranged from four months to forty-nine years, with an average of twenty years. The large majority were charity patients who came chiefly from the lower strata of society. In only 2 of the whole group could the previous antiluetic therapy have been considered as adequate, and in the remaining 52 cases treatment had been decidedly inadequate or lacking altogether.

The congenital group consisted of 4 males and 8 females, ranging from nine to thirty-three years of age, with an average age of nineteen years. Seven of these cases had received no antiluetic therapy whatever at the time of admission to the hospital, and the other five had been adequately treated only for the past three or four years.

All the cases included in this series were known to have syphilis, either from history, finding of definite syphilitic lesions, a positive Wassermann reaction or some combination of these. Any doubtful cases, or cases complicated by rheumatic heart disease, were excluded.

A complete study was made of each patient, including history, physical examination, orthodiagram, and electrocardiogram. The blood Wassermann reaction was determined in every case, and the spinal fluid was examined in about two-thirds of the cases. The heart size was determined by the orthodiascopic method, the frontal area and transverse diameter being measured and compared with the predicted normal as calculated on the basis of the age, height and weight of the individual. The deviation from the predicted normal was expressed in percentage, and the normal range was considered to lie within the limits of plus and minus 10 per cent.

RESULTS

Table I gives a summary of the findings in the group with acquired syphilis.

Incidence of Aortitis.—Of the 40 males in the acquired syphilitic group, only 2 showed no evidence of aortitis. One of these had been infected two years and the other fifteen years previously. Neither had received adequate treatment. An aortitis of slight degree was found in 11 (27.4 per cent), moderate in 13 (32.5 per cent), and marked in 14 (35.1 per cent). Of the 14 females, 3 showed no evidence of aortitis. Two of these were still in the secondary stage having been infected less than three months, and the third gave no history of a primary lesion, thus rendering it impossible to determine the duration. Of the remaining 11, an aortitis of slight degree was found in 2, moderate in 7, and marked in 2. Aortitis of some degree was found in 95 per cent of the males, 78.6 per cent of the females, or 90.7 per cent of the total. Nineteen of the males were fifty years old or over, and of these the aortitis was considered to be consistent with the age of the patient in 6 cases, and more marked than would be expected in 13. Five of the females were fifty years old or over, and of these 2 showed an aortitis consistent with the age, while 3 showed a more marked process.

The period required for the development of a demonstrable degree of aortitis appears to be very variable. In one man of twenty-one years, who had received his initial lesion two years previously and who had been treated over a period of nine months, no aortitis was found. Another man, twenty-six years of age, who had been infected two and one-half years before and who had received treatment for eighteen months following the primary lesion, showed evidence of an early aortitis. A third man, fifty-one years old, who had contracted the disease fifteen years before, and who had received very inadequate treatment had no signs of aortitis.

Of the four males in the congenital group (Table II), only one showed no evidence of aortitis, while the other 3 exhibited early signs and were classified as slight. Of the eight females with congenital syphilis, 6 had no signs of aortitis, while the remaining two were classified as having a moderate degree. These two were aged twenty-two and thirty-three years respectively, and with one exception were the oldest of the group. The oldest of those not showing signs of aortitis was twenty-four. Fifty-eight and four-tenths per cent of all the congenital cases showed no signs of aortitis, leaving 41.6 per cent with evidence of a slight or moderate degree. A marked degree of aortitis was not found in any of this group.

Incidence of Aneurysm.—A diagnosis of aortic aneurysm was made in 7 of the males with acquired syphilis, and in 3 of the females, making a total of 10, or 18.5 per cent. The earliest period at which an

TABLE I
FLUOROSCOPIC FINDINGS IN FIFTY-FOUR CASES OF ACQUIRED SYPHILIS

| NO. OF CASES | AGE YEARS | | DURATION OF INFECTION | | FLUOROSCOPIC EVIDENCE OF AORTITIS | | | | | | | | | | ANEURYSM | | | | HEART SIZE | | | | | | |
|--------------|-----------|------|-----------------------|------|-----------------------------------|------|--------|------|----------|------|--------|------|-----|------|----------|------|-------|------|------------|------|----------|--|--|--|--|
| | LIMITS | AVE. | LIMITS | AVE. | NONE | | SLIGHT | | MODERATE | | MARKED | | NO. | | % | | SMALL | | NORMAL | | ENLARGED | | | | |
| | | | | | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| Males | | | | | | | | | | | | | | | | | | | | | | | | | |
| 40 | 21-74 | 49 | 2-49 | 22.4 | 2 | 5.0 | 11 | 27.4 | 13 | 32.5 | 14 | 35.1 | 7 | 17.5 | 5 | 12.5 | 18 | 45.0 | 17 | 42.5 | | | | | |
| Females | | | | | | | | | | | | | | | | | | | | | | | | | |
| 14 | 18-60 | 40 | 1/2-22 | 12.0 | 3 | 21.4 | 2 | 14.3 | 7 | 50.0 | 2 | 14.3 | 3 | 21.4 | 5 | 35.7 | 5 | 35.7 | 4 | 28.6 | | | | | |
| Total | | | | | | | | | | | | | | | | | | | | | | | | | |
| 54 | 18-74 | 47 | 1/2-49 | 20.0 | 5 | 9.3 | 13 | 24.1 | 20 | 37.0 | 16 | 29.6 | 10 | 18.5 | 10 | 18.5 | 23 | 42.6 | 21 | 38.9 | | | | | |

TABLE II
FLUOROSCOPIC FINDINGS IN TWELVE CASES OF CONGENITAL SYPHILIS

| NO. OF CASES | AGE YEARS | | FLUOROSCOPIC EVIDENCE OF AORTITIS | | | | | | | | | | | | ANEURYSM | | | | HEART SIZE | | | | | | | | | | | | | |
|--------------|-----------|-------|-----------------------------------|--|------|------|-----|------|--------|------|-----|---|----------|---|----------|---|--------|---|------------|---|-----|---|-----|------|-----|------|-----|---|-----|--|---|--|
| | LIMITS | | AVE. | | NONE | | | | SLIGHT | | | | MODERATE | | | | MARKED | | | | NO. | | % | | NO. | | % | | NO. | | % | |
| | | | | | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | NO. | % | | | | |
| Males | 4 | 9-30 | 18 | | 1 | 25.0 | 3 | 75.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 50.0 | 2 | 50.0 | 0 | 0 | | | | |
| Females | 8 | 12-33 | 20 | | 0 | 75.0 | 0 | 0 | 2 | 25.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 25.0 | 6 | 75.0 | 0 | 0 | | | | |
| Total | 12 | 9-33 | 19 | | 7 | 58.4 | 3 | 25.0 | 2 | 16.6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 33.3 | 8 | 66.7 | 0 | 0 | | | | |

aneurysm was found was twelve years after the onset of the disease. One woman of thirty years who had been infected twelve years previously and had received almost no treatment, had a small aneurysm of the ascending aorta. A man of fifty-two years who gave a history of an initial lesion twelve years before, had a large aneurysmal sac of the ascending aorta. In the other cases in which aneurysm was found, the duration of the infection ranged from twenty-two to thirty-two years. None of the congenital cases showed any signs of sacculation.

Heart Size.—As previously explained, the frontal area and the transverse diameter of the heart were orthodiagraphically measured in each case and compared with the predicted normal. Table I shows the variation in the heart size in the various groups. Cardiac enlargement (area above +10 per cent) was present in 17 (42.5 per cent) of the males, and in 4 (28.5 per cent) of the females, making a total of 21, or 38.9 per cent, of the entire group. Five of the males and an equal number of the females had hearts below -10 per cent in area, making a total of 10, or 18.5 per cent. The heart size lay within the normal range (-10 to +10) in 18 of the males and 5 of the females making a total of 23, or 42.6 per cent. In the congenital group, none of the hearts were found to be enlarged. Seven (63.6 per cent) were in the normal range while 4 (36.4 per cent) were below normal size.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

Of special interest was a group of 23 patients, 19 males and 4 females, who were suffering primarily from syphilis of the central nervous system, and who were on the neurological service with diagnoses of general paresis, tabes dorsalis, taboparesis and meningovascular syphilis. The findings for this group are summarized in Table III. These patients ranged from thirty to sixty-two years of age, with an average of forty-five years. The average duration of the infection was twenty years, the limits being ten and twenty-six years. None of these had been adequately treated previously. Aortitis could be demonstrated in all of the males and in 3 of the 4 females, making a total of 22, or 95.7 per cent. Four males and 1 female showed a definite aneurysm of the aorta, making a total of 5, or 21.8 per cent. It is unsafe to draw conclusions from such a small number, but it is interesting to note that in this particular series the group classed as syphilis primarily of the central nervous system showed a higher incidence of aortitis and aneurysm than did the entire group composed of patients with acquired syphilis of all types. Only 7 (30.2 per cent) showed cardiac enlargement. In 13 (56.7 per cent) the heart size was within the normal range, and 3 (13.1 per cent) had hearts below normal size. Sixteen (69.7 per cent) showed definite cardiac involvement clinically, and aortic regurgitation was present in 3 (13.1 per cent) of this group.

TABLE III
FLUOROSCOPIC FINDINGS IN TWENTY-FOUR PATIENTS WITH SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

| NO. OF CASES | AGE YEARS | | DURATION OF INFECTION | | FLUOROSCOPIC EVIDENCE OF AORTITIS | | | | | | | | ANEURYSM | | HEART SIZE | | | | | |
|--------------|-----------|------|-----------------------|------|-----------------------------------|------|--------|------|----------|------|--------|------|----------|------|------------|------|--------|------|----------|------|
| | LIMITS | AVE. | LIMITS | AVE. | NONE | | SLIGHT | | MODERATE | | MARKED | | NO. | % | SMALL | | NORMAL | | ENLARGED | |
| | | | | | NO. | % | NO. | % | NO. | % | NO. | % | | | NO. | % | NO. | % | | |
| Males | | | | | | | | | | | | | | | | | | | | |
| 19 | 36-62 | 47 | 10-26 | 21 | 0 | 0 | 7 | 36.8 | 6 | 31.6 | 6 | 31.6 | 4 | 21.0 | 1 | 5.2 | 12 | 63.2 | 6 | 31.6 |
| Females | | | | | | | | | | | | | | | | | | | | |
| 4 | 30-54 | 45 | 12-20 | 16 | 1 | 25.0 | 1 | 25.0 | 2 | 50.0 | 0 | 0 | 1 | 25.0 | 2 | 50.0 | 1 | 25.0 | 1 | 25.0 |
| Total | | | | | | | | | | | | | | | | | | | | |
| 23 | 30-62 | 46 | 10-26 | 20 | 1 | 4.3 | 8 | 31.8 | 8 | 34.8 | 6 | 26.1 | 5 | 21.8 | 3 | 13.1 | 13 | 56.7 | 7 | 30.2 |

TABLE IV
CLINICAL FINDINGS IN FIFTY-FOUR CASES OF ACQUIRED SYPHILIS

| NO. OF CASES | AGE YEARS | | DURATION OF INFECTION | | ANTILUETIC TREATMENT | | AORTIC REGURG. | | CARDIAC INVOLVEMENT | | BLOOD PRESSURE | | | | POSITIVE WASSERMANN | | | | ONS LUES | |
|--------------|-----------|------|-----------------------|------|----------------------|--------------|----------------|------|---------------------|------|----------------|------|----------|------|---------------------|------|-----------|------|----------|------|
| | LIMITS | AVE. | LIMITS | AVE. | ADE- QUATE | INADE- QUATE | NO. | % | NO. | % | NORMAL | | ELEVATED | | BLOOD | | SP. FLUID | | NO. | % |
| | | | | | | | | | | | NO. | % | NO. | % | NO. | % | NO. | % | | |
| Males | | | | | | | | | | | | | | | | | | | | |
| 40 | 21-74 | 49 | 2-49 | 22.4 | 1 | 39 | 7 | 17.5 | 29 | 72.5 | 31 | 79.5 | 8 | 20.5 | 23 | 59.0 | 14 | 46.7 | 20 | 50.0 |
| Females | | | | | | | | | | | | | | | | | | | | |
| 14 | 18-60 | 40 | 1½-22 | 12.0 | 1 | 13 | 2 | 14.3 | 10 | 71.5 | 9 | 75.0 | 3 | 25.0 | 11 | 78.6 | 4 | 57.2 | 5 | 35.7 |
| Total | | | | | | | | | | | | | | | | | | | | |
| 54 | 18-74 | 47 | 1½-49 | 20.0 | 2 | 52 | 9 | 16.6 | 39 | 72.3 | 40 | 78.5 | 11 | 21.5 | 34 | 63.0 | 18 | 48.7 | 25 | 44.5 |

*Per cent of cases in which spinal puncture was done.

TABLE V
CLINICAL FINDINGS IN TWENTY-THREE CASES OF SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

| NO. OF CASES | AGE YEARS | | DURATION OF INFECTION | | ANTILUETIC TREATMENT | | AORTIC REGURG. | | CARDIAC INVOLVEMENT | | BLOOD PRESSURE | | | | POSITIVE WASSERMANN | | | |
|--------------|-----------|------|-----------------------|------|----------------------|-------------|----------------|------|---------------------|------|----------------|-------|----------|-----|---------------------|------|-----------|-------|
| | LIMITS | AVE. | LIMITS | AVE. | ADE-QUATE | INADE-QUATE | NO. | % | NO. | % | NORMAL | | ELEVATED | | BLOOD | | SP. FLUID | |
| | | | | | | | | | | | NO. | % | NO. | % | NO. | % | NO. | % |
| Males 19 | 36-62 | 47 | 10-26 | 21 | 0 | 19 | 2 | 10.5 | 13 | 68.5 | 17 | 94.7 | 1 | 5.3 | 11 | 58.0 | 13 | 68.5 |
| Females 4 | 30-54 | 45 | 12-20 | 16 | 0 | 4 | 1 | 25.0 | 3 | 75.0 | 4 | 100.0 | 0 | 0 | 1 | 25.0 | 4 | 100.0 |
| Total 23 | 30-62 | 46 | 10-26 | 20 | 0 | 23 | 3 | 13.1 | 16 | 69.7 | 21 | 95.5 | 1 | 4.5 | 12 | 52.2 | 17 | 74.0 |

TABLE VI
CLINICAL FINDINGS IN TWELVE CASES OF CONGENITAL SYPHILIS

| NO. OF CASES | AGE YEARS | | ANTILUETIC TREATMENT | | AORTIC REGURG. | | CARDIAC INVOLVEMENT | | BLOOD PRESSURE | | | | POSITIVE WASSERMANN | | | | CNS LUES | |
|--------------|-----------|------|----------------------|------------|----------------|---|---------------------|------|----------------|-------|----------|------|---------------------|-----|-----------|------|----------|------|
| | LIMITS | AVE. | ADEQUATE | INADEQUATE | NO. | % | NO. | % | NORMAL | | ELEVATED | | BLOOD | | SP. FLUID | | NO. | % |
| | | | | | | | | | NO. | % | NO. | % | NO. | % | NO. | % | | |
| Males 4 | 9-30 | 18 | 0 | 4 | 0 | 0 | 0 | 0 | 4 | 100.0 | 0 | 0 | 4 | 100 | 2 | 50.0 | 3 | 66.7 |
| Females 8 | 12-33 | 20 | 0 | 8 | 0 | 0 | 3 | 37.5 | 7 | 87.5 | 1 | 12.5 | 8 | 100 | 2 | 25.0 | 4 | 50.0 |
| Total 12 | 9-33 | 19 | 0 | 12 | 0 | 0 | 3 | 25.0 | 11 | 91.7 | 1 | 8.3 | 12 | 100 | 4 | 33.3 | 7 | 58.4 |

MISCELLANEOUS

A number of items of interest, such as the incidence of cardiac involvement, aortic regurgitation, hypertension, and positive Wassermann reactions for the entire group, which lie outside the scope of this paper, will be found recorded in Tables IV, V and VI, and may be of some value to those working on other phases of this subject. The heart was considered to be involved whenever there was cardiac enlargement, physical signs of heart disease, or definite electrocardiographic changes. A diagnosis of hypertension was made whenever the systolic pressure was over 150 or the diastolic over 100 mm. of mercury.

GROUP OF QUESTIONABLE ETIOLOGY

During the course of this study seven cases came under observation, in which there was a demonstrable degree of aortitis but no history or clinical evidence of either syphilitic or rheumatic infection. There were 4 males and 3 females, the ages ranging from eighteen to fifty years, with an average of thirty-five years. The degree of involvement was slight in 2, moderate in 4 and marked in 1. All but one had cardiac symptoms. Aortic regurgitation was present in 2, and the heart showed slight involvement in one case, moderate involvement in 3, marked involvement in 1, and appeared normal in 2. The patient who had no symptoms was a girl of eighteen years, with aortic regurgitation, a moderate degree of aortitis, fairly marked cardiac enlargement and a definitely pathological electrocardiogram. One woman of fifty years, with negative past history, had an aortitis definitely more marked than would be expected at that age, and the electrocardiogram showed a bundle-branch block. The blood Wassermann was repeatedly negative, and there was no other evidence of a syphilitic infection. Another case, a man of fifty years, with aortic regurgitation, had a small aneurysm of the ascending aorta, and the electrocardiogram showed complete heart-block. As in the rest of this group, the Wassermann reaction was negative, and no other evidence of syphilis could be found. No explanation for these cases is offered, but the question is brought up as to whether there may not be some other etiological factor in the production of changes in the aorta in addition to those with which we are familiar at the present time.

NECROPSIES

Three of the patients in the acquired syphilitic group died in the hospital and came to autopsy. The first case, a man of fifty years who gave a history of an initial lesion twenty-five years before, was on the neurological service with a diagnosis of tabes dorsalis. Cardiac symptoms were marked. On fluoroscopic examination the aorta was found

to be greatly dilated and a large aneurysm of the transverse arch could be visualized. The patient later died of heart failure and at post-mortem examination two aneurysms were found, one of the transverse arch and a very large one in the descending aorta situated directly behind the heart in such a manner that on fluoroscopic examination the shadow of the aneurysm had fused with that of the heart to such an extent that it was impossible to distinguish them.

The second case was that of a man of fifty-three years who gave no history of a syphilitic infection and had never known he had the disease. The blood Wassermann was positive, and on fluoroscopic examination a marked degree of aortitis was noted, as well as a large aneurysm of the transverse arch. This patient later died of congestive failure, and post-mortem examination revealed a marked syphilitic aortitis with a large aneurysm involving the transverse arch and the first portion of the descending aorta.

The third case was that of a man of seventy-four years who gave a definite history of syphilitic infection forty-nine years before. He had received very little antiluetic therapy. He complained chiefly of dyspnea and a chronic cough. The blood Wassermann was positive. On fluoroscopic examination a marked degree of aortitis was found, but no aneurysm formation. A diagnosis of syphilitic aortitis was made. The patient later died, and at necropsy the aorta showed no evidence of a syphilitic process but a moderate degree of arteriosclerotic change. The cause of death was found to be primary carcinoma of the lung. This case was instructive in that it demonstrated the possibility of the aorta escaping involvement in the presence of a syphilitic infection with positive Wassermann over a period of nearly fifty years.

SUMMARY AND CONCLUSIONS

1. A series of 54 cases of acquired and 12 cases of congenital syphilis are presented with special reference to the fluoroscopic findings in the heart and aorta.
2. Fluoroscopic evidence of aortitis was found in 90.7 per cent of the cases of acquired syphilis and in 36.4 per cent of the cases of congenital syphilis.
3. Aneurysm of the aorta was found in 18.5 per cent of the cases of acquired syphilis and was absent in all of the congenital cases.
4. Cardiac enlargement was present in 38.9 per cent of the cases of acquired syphilis.
5. In a group of 23 cases of acquired syphilis, exhibiting primarily central nervous system disease, 95.7 per cent showed evidence of aortic involvement, and aneurysm could be demonstrated in 21.8 per cent.

DISCUSSION

Dr. L. A. Conner, New York, N. Y.—As I understand this, it was purely a fluoroscopic study. When therefore Doctor Kurtz says that a certain large percentage of the patients showed signs of syphilitic aortitis it seems to me he must mean that they showed changes from his conception of the normal fluoroscopic picture, which he interpreted as being evidences of aortitis. If that is the case I submit that the two things are not necessarily synonymous.

Dr. H. E. B. Pardee, New York, N. Y.—I would like to hear in more detail what were the criteria used for the diagnosis of aortitis in this report.

Dr. Kurtz (closing).—I used the term aortitis in a broad sense to denote any demonstrable changes in the aorta, the criteria for such a diagnosis being: (1) elongation or tortuosity, (2) widening of any portion, (3) pulsation to the right of the sternum, and (4) increased density permitting visualization of the descending aorta, especially in patients under the age of fifty years. It is ordinarily not possible to distinguish between the syphilitic and arteriosclerotic types of aortitis on fluoroscopic examination. This was well illustrated in the case mentioned at the close of the paper. The patient was a man of seventy-two years who gave a definite history of syphilitic infection about fifty years previously. The blood Wassermann was positive, and on fluoroscopic examination the aorta showed very definitely the changes which are ordinarily associated with an aortitis. I boldly made a diagnosis of syphilitic aortitis, but when the patient died and came to autopsy, the process was purely arteriosclerotic in type, and no syphilitic changes were found. Since then I have been careful not to make an etiological diagnosis on the basis of fluoroscopic appearance. The only difference in the appearance of the aorta with aneurysm is a localized sacculum in addition to the other criteria mentioned above.

FURTHER STUDIES OF THE AORTA WITH SPECIAL REFERENCE TO LUETIC AORTITIS

A. O. HAMPTON, M.D., E. F. BLAND, M.D., AND
HOWARD B. SPRAGUE, M.D.
BOSTON, MASS.

A METHOD for determining the presence or absence of abnormal dilatation of the aorta has been a subject of considerable interest for both clinical and roentgenological investigators. Repeated attempts have been made at the Massachusetts General Hospital by various workers to standardize some practical method of determining the size of the ascending and transverse portion of the thoracic aorta.

In this paper we are continuing the study recently reported by Hampton and Jones¹ in which a method was presented for the determination of aortic dilatation. In the earlier paper the left anterior oblique view of the aorta taken at seven feet tube-screen distance, with the aid of fluoroscopy at the same distance, was reviewed in a selected group of 120 cases. In this group, 84 patients were suspected clinically of having luetic aortitis. Seventeen other cases were selected because the aorta appeared to be visible in the left anterior oblique teleroentgenogram. None of these latter cases was considered clinically abnormal except for the presence of arteriosclerosis. The age group of the 17 cases ranged from forty to sixty years, being well within the usual luetic aortitis age limit. In the remaining 19 cases of the group of 120, hypertension was considered to be the cause of aortic dilatation, although 4 had positive Wassermann reactions and 7 had aortic regurgitation. The result of the above investigation seemed to justify the deduction of a normal and abnormal average measurement of the aortic root shadow and aortic arch. The arteriosclerotic aortic root shadow was found to be no more than 6 cm. in diameter and in the dilated aorta group was invariably over 6 cm. in diameter. A clinical and roentgenological agreement of 79.8 per cent of the cases was established.

The method employed in the present study is the same as the one previously described by Hampton and Jones.¹

Standard teleroentgenograms are taken of each case studied with the patient in three positions: antero-posterior, right anterior oblique and left anterior oblique, of which the latter has been found to be the most valuable.

For the left anterior oblique view, the patient is placed at an angle of from forty to fifty degrees with the central beam of the x-ray. This position is best obtained by direct observation with seven foot fluoroscopy. Under direct roentgenoscopic observation, the patient is rotated to the right with the left nipple and left shoulder in approximation with the fluorescent screen until the bright space behind the ascending aorta and below the aortic arch is most clearly seen. The right arm is then brought forward over the top of the screen, the right wrist of the

patient is grasped by the examiner and rotated medially as it is pulled upward and forward. Care must be taken to maintain the semilateral position. This maneuver results in drawing the right scapula forward and upward and causes the right intercostal spaces to widen, thus giving the maximum clearness of the aorta in so far as it is visible. The fluoroscopic screen is then replaced by the radiographic cassette. The tube is centered at the fourth dorsal vertebra. The patient is instructed to take and hold a deep breath. The exposure time should be as short as possible, preferably 1/10th to 1/20th of a second. The fluoroscopic observation of the pulsation and relative size of the aorta together with the impression obtained during the course of the examination is very important. A seven foot fluoroscope is not necessary for proper posing of the patient. Many satisfactory examinations have been made without its use. The right oblique view of the aorta is obtained in much the same manner except that an effort is made to superimpose the ascending and descending aorta by rotating the patient in the opposite direction, the proper angle between the line of the shoulders and the central beam being approximately thirty degrees.

Measurements of the supracardiac shadow obtained from the teleroentgenogram are made in the anteroposterior and left anterior oblique views. The anteroposterior projection is measured by a transverse line across the widest point of the supracardiac silhouette above the region of the pulmonary artery. The aorta is considered to be abnormal if this transverse measurement exceeds 6 cm. and is not explained by tortuosity of the aorta, obesity, high diaphragm, or mediastinal mass.

The radiograph obtained with the patient in the left anterior oblique position must be carefully studied. It is necessary to identify the arch of the aorta, the trachea, and the posterior border of the heart. The arch is best seen where it is crossed by the trachea and left main bronchus. The posterior border of the heart can usually be traced upward from the apex to the region of the pulmonary artery. The inferior margin of the arch of the aorta is then followed anteriorly and downward to the region of the pulmonary artery where it intersects the posterior border of the heart. This is often difficult unless the radiograph is of excellent quality and the examiner has had considerable experience. The pulmonary artery should be identified if possible, and when there is no doubt of its identity, the method of measurement suggested by O'Kane, Andrew, and Warren² has been found to be valuable. When the pulmonary artery is not visualized, as is often the case, the visible portions of the posterior border of the ascending aorta must be projected downward to meet the line of the posterior border of the heart. This intersection is in the anatomical location of the pulmonary artery and is taken as the posterior point of a transverse line to be drawn from the junction of the ascending aorta with the anterior border of the heart. The shadow of the anterior margin of the ascending aorta and the curve of the silhouette of the anterior border of the heart are easily identified. The length of the transverse line drawn between the above points rarely exceeds 6 cm., unless the aorta is abnormally dilated. It must be borne in mind that this diameter is not the true diameter of the aorta as it is found at post-mortem examination. It is merely an arbitrary measurement of the aortic root shadow which we believe to vary directly as the diameter of the aorta. We do not know the absolute diameter of the aorta as it exists when the arterial blood pressure is maintained, since such a direct measurement has rarely if ever been made. The diameter of the normal aorta as measured at post-mortem examination is not usually over 3 cm. The arch of the aorta may be measured in most cases, and this diameter does not exceed 3.5 cm. unless the aorta is dilated.

Using the above method, we have studied for the present report an additional series of 89 cases referred for roentgenological examination of the heart and great vessels because cardiovascular disease was sus-

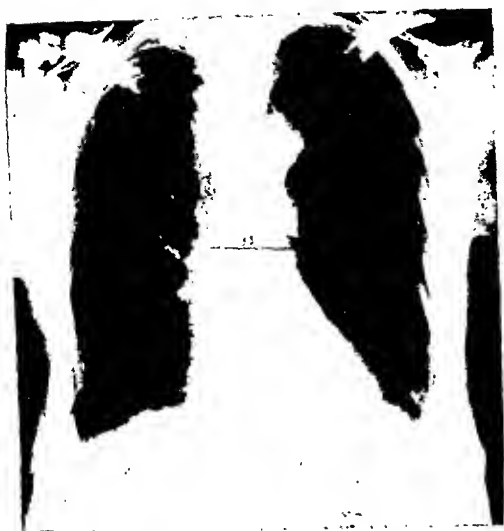


Fig. 1-A.



Fig. 1-B.

Fig. 1 *A* and *B*.—*A*, Antero-posterior teleroentgenogram of arteriosclerotic aorta showing tortuosity without dilatation. *B*, Oblique teleroentgenogram of arteriosclerotic aorta. The aorta is unusually well shown. The measurements are within normal limits. Note points of measurement of ascending and arch portions of the aorta.



Fig. 2-A.



Fig. 2-B.

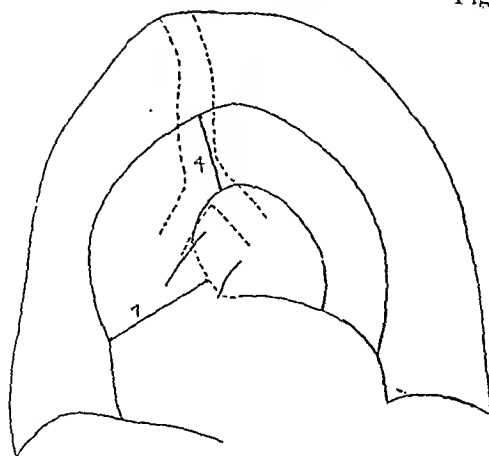


Fig. 2-C.

Fig. 2 *A*, *B* and *C*.—*A*, Antero-posterior teleroentgenogram of a dilated aorta. *B*, Left anterior oblique teleroentgenogram showing typical measurements of ascending and arch portions of the aorta. *C*, Tracing of *B*, showing typical measurements.

pected clinically. These examinations were done routinely in an effort to determine whether or not the measurement of the aortic root shadow in the left anterior oblique view is sufficiently reliable to be of practical value. The measurements were done before a correlation with clinical impressions had been made. This nonbiased attitude of the examiner was suggested as a contrast to that in the study of 120 cases previously reported in which a dilated aorta was anticipated in a relatively large percentage.

MEASUREMENT OF AORTIC ROOT SHADOW AND ARCH

| | |
|---|-----------------|
| Number of cases ----- | 89 |
| Number of cases with abnormally dilated aorta by roentgen-ray examination ----- | 15 |
| A. Clinically diagnosed luetic ----- | 11 |
| B. Nonluetic ----- | 4 |
| | |
| AORTIC ROOT SHADOW | |
| ASCENDING AORTA | |
| ARCH | |
| Average transverse diameter of the 11 luetic aortas ----- | 7.0 cm. 4.6 cm. |
| Average transverse diameter of the 4 nonluetic dilated aortas ----- | 6.8 cm. 3.7 cm. |
| Average transverse diameter of nondilated aortas ----- | 5.3 cm. 3.3 cm. |
| Maximum normal transverse diameter ----- | 6.0 cm. 3.5 cm. |

In the left anterior oblique view of the 89 cases, the transverse measurement of the aortic root shadow or ascending aorta exceeded the normal in 15, of which 11 were considered syphilitic, 2 had definite hypertension, 1 had marked arteriosclerosis, and 1 had arteriosclerosis and slight aortic regurgitation. Of the 11 cases with dilatation of the aorta by roentgenological examination, and in which lues was clinically considered the etiological factor, 6 had both a positive Hinton reaction of the blood serum and an aortic regurgitation. In 3 cases, the x-ray demonstration of a dilated aorta together with a positive Hinton reaction seemed sufficient evidence to warrant the clinical diagnosis of luetic aortitis in the absence of other possible etiological factors, such as hypertension or arteriosclerosis. In the remaining 2 patients, the presence of aortic regurgitation with a history of primary syphilitic infection even in the absence of a positive reaction of the blood serum was considered sufficient evidence for a diagnosis of luetic aortitis. The 4 remaining cases with the transverse measurement of the ascending aorta exceeding 6 cm., 2 had hypertensive heart disease, and 2 had arteriosclerotic heart disease clinically. It is of considerable interest that there were in this series 33 cases with definite hypertension but that only 2 showed evidence of aortic dilatation.

SUMMARY

The method of study of the aorta now in use at the Massachusetts General Hospital is presented. This method, we believe, is valuable in determining the presence or absence of aortic dilatation even in cases

where the clinical impression is not known to the roentgenologist. Roentgenoscopy at a seven foot tube-screen distance is considered a valuable aid to accurate positions for the teleroentgenogram. Teleroentgenography in the left anterior oblique position has been found to give valuable evidence of aortic dimensions. The points of measurement selected are described and are thought to be of practical application.

Measurements of the aorta in a series of routine radiographs compared with the clinical findings seem to justify the deduction of a normal and abnormal average. The normal and arteriosclerotic ascending aorta without dilatation was found to average 5.3 cm. The dilated ascending aorta invariably measures over 6 cm. in diameter when estimated by the method presented. The differential diagnosis in cases found by roentgen examination to have aortic dilatation depends upon clinical and other roentgen findings.

REFERENCES

1. Hampton, A. O., and Jones, T. D.: A Clinical and Roentgenological Study of the Aorta, With Special Reference to Luetic Aortitis, *Am. J. Roentgenol.*, 23: 390, 1930.
2. O'Kane, Geo. H., Andrew, Fred D., and Warren, Stafford L.: A Standardization Roentgenologic Study of the Heart and Great Vessels in the Left Oblique View, *Am. J. Roentgenol.*, 23: 373, 1930.
3. Assman, H.: Klinische Röntgendiagnostik der inneren Erkrankungen, Leipzig, 1929, F. C. W. Vogel.
4. Frik, K.: Zur Deutung des Röntgenbildes im ersten schrägen Durchmesser. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 29: 723, 1922.
5. Holmes, G. W., and Ruggles, H. E.: *Roentgen Interpretation*, Ed. 3, Philadelphia, 1926, Lea and Febiger.
6. Holzknecht, G.: Das radiographische Verhalten der normalen Brustaorta. *Wien. klin. Wchnschr.*, 13: 225, 1900.
7. Ledbetter, P. V., Holmes, G. W., and White, P. D.: The Value of the X-ray in Determining the Cause of Aortic Regurgitation. *AM. HEART J.*, 1: 196, 1925.
8. Martin, C. L.: Roentgen-Ray Cardiac Studies. *Am. J. Roentgenol.*, 8: 295, 1921.
9. Reich, L.: Das Röntgenbild und die orthodiographische Messung der Aorta im zweiten schrägen Durchmesser. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 34: 322 and 472, 1926.

THE ELECTROCARDIOGRAM AND TELEROENTGENOGRAM IN EARLY SYPHILIS*

RUTH INGRAM, M.D., AND EDWIN P. MAYNARD, JR., M.D.
BROOKLYN, N. Y.

WHEN one studies the literature dealing with the heart and aorta in early syphilis, one finds great divergence of opinion as to the frequency with which clinical, electrocardiographic and x-ray evidence of involvement of these organs is to be found. The earlier writers in general seemed to find symptoms and signs of invasion of the heart and aorta in a much higher percentage of the early cases than do the more recent investigators. This is quite striking and suggests the thought that the change may be due, not only to better instruments of precision, but also to the use of more rigid criteria for the diagnosis of syphilis of the heart. For example, Grassman¹ in 1900 detected arrhythmia in 85 per cent, and murmurs in 40 per cent of 288 cases of secondary syphilis. Harlow Brooks² in 1921 found that out of 300 cases of syphilitic heart disease, 8 per cent showed cardiac involvement in the secondary stage. Howard³ in 1924 stated that of fifty patients in the secondary stage, eight complained of palpitation, five of cardiac pain, and three of dyspnea; one had edema. In 1926 Wilson, Wile, Wishart and Herrmann⁴ said that "a study of about sixty patients with primary and secondary lues has convinced us that reliable clinical or electrocardiographic evidence of involvement of the heart or aorta during this stage of the disease is decidedly rare." Turner and White⁵ in 1927 made a very careful study of fifty cases of primary and secondary syphilis. They excluded from their series all cases of rheumatic heart disease, arteriosclerosis, hypertension, hyperthyroidism, or any other condition that might affect the heart, and limited their cases to patients under forty years of age. A complete study of these cases, including history, physical examination, electrocardiogram and x-ray examination showed no definite clinical evidence of disease of the heart or aorta. Finally, Arnett⁶ in 1928 found that organic cardiovascular disease was not demonstrably present in any of the twenty-five secondary syphilis patients studied.

Thus, it is apparent that the clinical diagnosis of syphilitic involvement of the heart and aorta in early lues was made much more frequently by the pioneer workers in this field than it is today.

In 1927, at the suggestion of Dr. Alfred Cohn, a study of syphilis of the heart and aorta was begun in the adult Cardiac Clinic at the

*From the Departments of Medicine and Radiology, the Brooklyn Hospital, Brooklyn, N. Y.

Brooklyn Hospital. The plan of work is somewhat as follows: Every patient admitted to the Brooklyn Hospital venereal disease clinic in whom a positive diagnosis of syphilis has been made is referred to the cardiac clinic for complete survey, including history, physical examination, x-ray of heart and electrocardiogram. The examinations are made by two men trained in cardiology, and the patients are enrolled in the cardiac clinic. Reexaminations are made at varying intervals, depending upon the conditions found, but all patients are reexamined at least once a year. It is planned to keep up this work indefinitely in order to study the development and course of syphilis of the cardiovascular system. The present study of the electrocardiogram and x-ray findings in early syphilis is a part of the research program.

In order to make our findings significant it was decided to select our cases very carefully. We chose for early cases only those who had had syphilis for a year or less, and we excluded all patients in whom the date of the initial lesion was not known. Second, in order to exclude the changes due to age, we limited our series to patients under forty years. Third, to rule out hypertension, we included no case with a systolic blood pressure over 140 mm. Lastly, we excluded all patients who gave a history of any other disease that might affect the heart, including rheumatic fever, chorea and hyperthyroidism. As a result, our study, which began with fifty-five early cases, rapidly dwindled to a total of twenty-seven that fulfilled all the requirements.

Of these 27 cases, 19, or 70.4 per cent, gave electrocardiograms that fell within the limits of normal, 8, or 29.6 per cent, showed a left axis deviation, including one with premature ventricular beats as well. Compared with the findings in the series of cases of early syphilis studied by Turner and White,⁵ the incidence of left axis deviation is much higher. They found only one instance in fifty cases, or 2 per cent. Cohn⁷ in an investigation of the size of the heart in soldiers in 1920 found that of 208 normal soldiers six showed signs of left ventricular preponderance, an incidence of 2.8 per cent. Proger and Davis⁸ have recently published a study of axis deviation in normal hearts and found that 33 per cent showed a left axis deviation, varying from slight to marked degree. Our figure of 29.6 per cent in young adults with early syphilis corresponds very closely with this. The one instance of premature ventricular beats cannot safely be attributed to the syphilis because of the many factors that may cause this irregularity in young people. Therefore, when one considers the frequency with which left axis deviation may be found in normal hearts, one must conclude that our findings of 29.6 per cent in young adults with early syphilis falls within the limits of normal. This brings us to the conclusion that in our study of the electrocardiogram

in twenty-seven cases of early syphilis, no significant deviations from the normal were found.

Now let us turn to the examination of these hearts by the teleroentgenogram. The films were taken in the antero-posterior position at a six-foot distance from the target. The shadow measured for the aorta was that shadow seen immediately to the right and to the left of the spine in the region of the aorta. In those films in which the shadow to the right formed a straight line rather than a convex curve, it is very likely that we were not measuring the aorta but the vena cava, and that the ascending aorta was not seen. In measuring the size of the heart itself, the total transverse diameter was used and compared with the total diameter of the chest. A total diameter of the heart, 50 per cent of the total diameter of the chest, was considered the upper limit of normal. However, in the actual consideration of enlargement, the conformation of the chest and the position of the diaphragm were taken into account.

A total of twenty-three cases was studied in this way. Of these, ten were normal throughout. In not any of them was there any very striking change in the aortic shadow, but in six, or 26 per cent, there seemed to be slight but definite enlargement, especially of the ascending aorta.

When we attempted to correlate the electrocardiographic findings with the x-ray, we found that of the six cases of left axis deviation in which films were made, three were normal and three showed slight but definite enlargement of the aorta. The three cases of enlargement of the aorta that remained gave normal electrocardiograms. Therefore, there was no close correlation between electrocardiographic and x-ray findings in our series.

From a study of the x-ray films in the twenty-three cases of early syphilis we cannot state that the slight changes found in the aorta in six were due to the syphilis. It may be that changes such as these would be found in a similar series of normal individuals.

One point further we wish to emphasize. As stated before, we limited our series very carefully to individuals who had no other condition but syphilis. As we threw out case after case, the interesting changes in the electrocardiogram and x-ray film began to disappear, until finally when our series was perfect our abnormal findings disappeared.

SUMMARY AND CONCLUSIONS

1. A series of twenty-seven cases of early syphilis was studied electrocardiographically. The tracings were found to fall within the limits of normal.

2. Twenty-three of these cases were studied by teleroentgenogram. Six of them showed slight widening of the aorta which was not beyond the limits of normal deviation.

REFERENCES

1. Grassman, K.: *Deutsches Arch., f. klin. Med.*, 68: 455, 1900; 69: 58, 264, 1901.
2. Brooks, Harlow: *Am. J. Syph.*, 5: 217, 1921.
3. Howard, Tasker: *Am. J. M. Sc.*, 167: 266, 1924.
4. Wilson, Wile, Wishart, and Herrmann: *Proc. Soc. Exper. Biol. & Med.*, 23: 275, 1926.
5. Turner, K. B., and White, P. D.: *Arch. Int. Med.*, 39: 1, 1927.
6. Arnett, J. H.: *Am. J. M. Sc.*, 176: 65, 1928.
7. Cohn, A. E.: *Arch. Int. Med.*, 25: 499, 1920.
8. Proger, S. H., and Davis, D.: *Arch. Int. Med.*, 45: 974, 1930.

DISCUSSION

Dr. Herrmann, New Orleans, La.—I have had a case of pericarditis in a middle-aged patient with a severe roseolar rash of acute syphilis. The signs cleared up promptly under intensive arsphenamine therapy. I believe this was an acute syphilitic pericarditis and suggestive evidence that the pericardium may be involved in early syphilis. The Wassermann is still positive, but there are no evidences of cardiovascular syphilis. There were very slight changes in the T-wave of the electrocardiograms.

Dr. F. N. Wilson, Ann Arbor, Mich.—Some years ago Dr. Wile had several cases of primary and secondary lues in which he felt that involvement of the heart had occurred. He suggested that I examine a series of patients from his clinic from this standpoint. I examined approximately fifty patients with primary and secondary lues, when first seen, and again after the first course of arsphenamine. A physical examination was made, and an electrocardiogram was taken on each occasion. In not one of these patients did I find anything that led me to suspect that the heart was involved. Most of the patients were young and had no disease other than the infection for which they came to the clinic.

Dr. John Wyckoff, New York, N. Y.—I would like to ask about the P-R intervals and the QRS complex in this series.

Dr. Maynard (closing).—We studied the P-R interval, the QRS, the T-wave and the S-T interval in all our cases. There were no changes from the normal. I am interested in Dr. Wilson's series. We have not made a clinical study of our cases of early syphilis. We have not seen pericarditis as mentioned by Dr. Herrmann.

SYMPTOMS AND CLINICAL COURSE OF SYPHILITIC AORTIC INSUFFICIENCY*

R. W. SCOTT, M.D.
CLEVELAND, OHIO

THIS paper deals with the clinical observations on 107 autopsied cases of syphilitic aortic insufficiency seen on the wards of the Cleveland City Hospital during the past ten years. During this time a particular effort was made to correlate the clinical aspects of this disease with the post-mortem findings, in the belief that such a combined clinical and pathological study which brought the pathologist to the wards as well as the clinician to the laboratory, afforded the best method of attacking some of the problems associated with latent syphilis as a cause of heart disease.

Before considering the following observations, I think it important to mention that they were made on a group of patients in the charity wards of a municipal hospital. For the most part the patients were from the working class and more than 50 per cent were negroes. Many patients had advanced heart failure when first seen.

Sex.—There were 92 males and 15 females, a proportion of approximately six to one.

Age.—The youngest patient was twenty-three years old; the oldest seventy-nine years. The number of cases in the various decades is as follows:

| Decade | 20-30 | 30-40 | 40-50 | 50-60 | 60-70 | 70-80 |
|--------|-------|-------|-------|-------|-------|-------|
| | 5 | 25 | 32 | 27 | 15 | 3 |

Thus it is seen that the largest number of cases is in the decade, 40-50.

Interval from Primary Infection to Death.—The shortest interval elapsing from the primary infection to death was five years, the longest forty-eight years, with an average of about twenty years.

An effort was made to ascertain the length of time that free aortic regurgitation was present before the signs of myocardial failure appeared. This was admittedly difficult because the vast majority of our patients did not seek medical attention until signs of heart failure developed. In this series the longest interval that free aortic regurgitation was known to exist prior to the development of heart failure was six years. This was in a female whose insufficiency was due to ring dilatation with very slight involvement of the aortic leaflets. I have

*From the Medical Clinic of Western Reserve University at Cleveland City Hospital.

seen one patient whose insufficiency existed for at least eighteen years before death from heart failure.

Subjective Symptoms.—The first symptoms complained of by the vast majority of patients in this series were those of beginning heart failure—dyspnea on exertion, palpitation, and edema of the lower extremities. Precordial and substernal pain or anginal attacks were seldom noted except in those cases of marked narrowing of the coronary arteries. Even in the presence of marked constriction of the coronary mouths, chest pain was not always present. For example, in one instance of complete occlusion of both coronaries from syphilitic changes in the sinuses of Valsalva, pain was not present during the three weeks that the patient was under observation before death.

Objective Findings in the Absence of Congestive Failure.—In the majority of instances there were the well-known peripheral vascular signs of free aortic regurgitation; a thickened left ventricle with a forcible localized apical thrust, usually displaced downward and outward. More often than not a to-and-fro murmur was present, loudest over the anatomical site of the aortic orifice, but distinctly audible over the base and in the aortic area to the right of the sternum. Of the more unusual physical signs, there were two cases in this series in which the diastolic murmur was so loud as to be heard as a buzzing sound by the unaided ear several feet from the patient's bed. There was also in these two cases a marked diastolic thrill palpable over the base of the heart. In four cases a palpable systolic thrill was present, suggesting aortic stenosis, but in none of these was the aortic orifice narrowed at autopsy. In approximately 5 per cent of this series one heard over the aortic area a snappy second sound of valve closure, followed by a blowing diastolic murmur. This proved to be a valuable diagnostic sign of ring dilatation.

Objective Findings in the Presence of Congestive Failure.—In 99 cases in this series, varying grades of congestive heart failure were present at the time of death. With advancing failure the apical thrust usually became less sharply localized, and palpation over the apex revealed a more diffuse and less forcible left ventricle. At this stage the murmurs arising at the aortic orifice became less intense, and the pulse lost its characteristic water-hammer qualities. The cardiac mechanism remained normal in all but five cases. There were three instances of auricular fibrillation and two of paroxysmal auricular tachycardia. I have no accurate data on the incidence of periodic breathing in this group dying of heart failure, but certain it is that the majority had Cheyne-Stokes respiration for varying intervals preceding death.

Clinical Course.—An attempt was made to ascertain the duration of life after the onset of symptoms, but accurate information on this point was not possible in all cases. The longest interval noted was six

years, the shortest two weeks, with an average of about one year. To arrive at this average, I assumed that an individual occupied as a laborer possesses a certain myocardial reserve to permit him to carry on. If he is forced to stop work because of respiratory distress and in spite of treatment succumbs to his disease in less than a year, we are justified in including such a case in the group that died less than a year after the onset of symptoms.

The more or less abrupt appearance of cardiac symptoms, and the progressive nature of the heart failure characterized the clinical picture. For example, the following account covers the salient features observed in the clinical course of this group of patients: A well-developed male in the prime of life, with a negative cardiac history, always able to do manual labor, observes breathlessness on exertion and palpitation of the heart. These symptoms gradually increase in severity until he is no longer able to work. Edema of the lower extremities appears. At this stage he is admitted to the hospital, and one finds the cardinal signs of congestive failure: an enlarged and overactive left ventricle, with aortic insufficiency. In spite of treatment the patient may progress rapidly to death, or he may make a temporary recovery only to fail again in a few weeks or months. Certain it is that in the type of patient here considered a frank cardiac decompensation marks the beginning of the end. The majority died in less than a year from the onset of congestive failure, and it was the exceptional case that lived more than two years.

SUMMARY

Following are the conclusions reached from the clinical observations on 107 autopsied cases of syphilitic aortic insufficiency. It is probable that the type of patient included in this group—individuals from the working class, and the majority negroes—has some influence on the facts observed, though to what extent it is obviously difficult to determine.

1. Syphilitic involvement of the aortic orifice may appear as early as five years and as late as forty-eight years after the primary infection. The average time interval is around twenty years.

2. Free aortic regurgitation appearing out of a clear sky in an adult with a negative cardiac history, and with no evidence of acute infection, should be regarded as syphilis until proved otherwise.

3. Substernal pain and anginal attacks are not important symptoms in the type of cases here considered.

4. Syphilitic aortic insufficiency is more common in the negro than in the white.

5. The appearance of congestive heart failure in a patient with syphilitic aortic insufficiency is a grave omen.

DISCUSSION

Dr. F. N. Wilson, Ann Arbor, Mich.—Dr. Scott spoke of the cardiac pain which some of his patients had. He stated that in his series of cases it was relatively rare and occurred in cases in which the mouths of the coronary arteries were narrowed, and I presume that the pain was of the type referred to as angina pectoris. I have seen a few patients with syphilitic aortitis who complained of chest pain which appeared to be of a different kind. I would not venture to say that the type of pain which they had was characteristic. I remember two of these patients well; both had slight aortic insufficiency, a faint murmur without vascular signs, and slight dilatation of the first part of the aorta. The Wassermann was positive in both. They complained of a burning pain which was felt in the epigastrium or beneath the ensiform and radiated upward under the sternum. There was no radiation to other parts of the chest or to the arms. The pain was not closely related to exercise and was not relieved by nitroglycerin. Antihypertensive treatment had no definite effect upon the pain while the patients were under observation. The pain was quite different from that ordinarily seen in coronary disease and this suggested that it might be the direct result of the aortic involvement.

Dr. Emanuel Libman, New York, N. Y.—I will speak briefly on the subject of the sensitiveness to pain in the patient, which is important in this type of case. In the hyposensitive type of patient we may get contralateral radiation, or radiation toward the focus (inverse radiation). There may be very marked weakness instead of pain. That is a very important point. Reflex disturbance may largely replace pain. There may be aerophagia. A patient with coronary thrombosis may have this latter symptom with dyspnea. If Dr. Wilson's patient was hyposensitive, the pain might have radiated toward the heart, instead of outward. I agree with Dr. Wilson, I have not seen very much aortic syphilis.

Dr. Smith, Iowa City, Iowa.—I would like to know if Dr. Scott thinks involvement of the coronaries as important as aortic regurgitation.

Dr. Alexander Lambert, New York, N. Y.—Why does Dr. Scott say that the ring is dilated when the valve snaps hard and there is a blowing diastolic murmur? Is that not an evidence of the valve closing with thickened edges rather than of dilatation of the ring?

Dr. Sael.—I would like to ask Dr. Scott if he encountered any cases of nocturnal dyspnea. One-third of these cases will complain of difficulty in breathing at night. They begin with nightmares, advancing to real cardiac asthma attacks. If we bear that in mind, we can advance the period of symptoms six months. This precedes dyspnea on exertion and substernal pain.

Dr. W. H. Robey, Boston, Mass.—We had an interesting case at the Boston City Hospital. A colored washerwoman of thirty-four years who had to climb three flights of stairs to her tenement, came to the ward complaining of myocardial insufficiency. She had no pain. At autopsy both coronaries were found occluded, yet she had been climbing those stairs carrying the washing for six months with that condition.

Dr. Lewis A. Conner, New York, N. Y.—This is a very accurate description of a moderately progressive case of luetic aortitis after the advent of aortic insufficiency, and it is all the more striking when one contrasts it with the benign course of uncomplicated aortic insufficiency of rheumatic origin. That is the lesson to be drawn. These cases go downhill with rapidity and certainty. On the other hand, rheumatic patients live many years and often fill out their normal span of life.

Dr. James B. Herrick, Chicago, Ill.—In cases of syphilitic aortitis with aortic regurgitation, it is not necessarily true that there must be a rapid decline. I have seen two or three patients with syphilitic aortic regurgitation who lived for several

years; one patient lasted nine years then passed out of my observation. I agree with Dr. Wilson and Dr. Libman as to pain in this type of disease. It is not always typically anginal. I have seen pain corresponding to angina, but I have also seen patients who describe a burning, or discomfort, or gnawing sensation, which was not necessarily brought on by exertion. There are many forms of bizarre precordial distress. In regard to the sharply accented aortic second sound, it has a bell-like ringing quality, somewhat different from the sound of essential hypertension of atheroma. Why, I do not know. It is not always present, but when it is it suggests syphilitic aortitis.

Dr. R. W. Scott (closing).—In reply to Dr. Lambert's question concerning the snappy valve closure sound followed by a blowing diastolic murmur as evidence of ring dilatation, I will say that these physical signs occurred in several cases which at autopsy showed a dilated aortic ring with fairly normal valve cusps. In such instances the valves may be actually larger than normal. They are approximated during diastole, causing a snappy and sometimes a tympanitic sound, but being unable to seal the dilated orifice, a regurgitant stream of blood flows back into the left ventricle, causing a murmur. It is admittedly difficult to estimate the amount of leak that may occur at the site of widened commissures. Being at the periphery of the stream, it seems likely that less blood would regurgitate through widened commissures than through a defect in the center from insufficient valve surface.

Anginal pain and nocturnal dyspnea were seldom noted in this group of patients. On the other hand, these symptoms are known to occur in some cases of syphilitic aortitis. It seems likely that the nervous organization of the patient—the susceptibility to pain—is an important factor determining the presence or absence of pain in uncomplicated syphilitic aortitis.

I have seen three cases similar to those mentioned by Dr. Robey. Both coronary arteries were completely occluded from syphilitic involvement of the sinuses of Valsalva, without infarction of the myocardium. The long time interval mentioned by Dr. Herriek did not occur in this series so far as we could determine. We have no data on the duration of free aortic regurgitation preceding the appearance of myocardial failure, but certain it is that once congestive failure appears, the prognosis in the majority of cases is bad. Therapeutic measures may lead to temporary improvement, but in our experience a frank cardiac decompensation in a patient with syphilitic aortic insufficiency marks the beginning of the end.

THE DIAGNOSIS OF CARDIOVASCULAR SYPHILIS; ANALYSIS OF CLINICAL AND POST-MORTEM FINDINGS*

WILLIAM D. REED, M.D.
BOSTON, MASS.

SYPHILITIC lesions of the aorta were disclosed in 3.5 per cent of 1678 consecutive necropsies.¹ In 79.5 per cent of these cases the disease was advanced and in most was listed by the pathologist as the primary cause of death. In a later series² of 100 necropsies cardiovascular syphilis was found in 7 per cent. These studies of clinical records and examination of the literature showed cardiovascular syphilis to represent 11 to 25 per cent of all organic disease of the heart.

Syphilis of the heart and aorta, after a latent period of varying length, tends to become a progressive disease; it maims and kills those in the prime of life. There is evidence that if the disease be treated adequately at an early stage its disastrous effects often may be prevented. It should, therefore, be evident that the morbidity and mortality from cardiovascular syphilis are in certain respects a reproach to the medical profession.

Greater accuracy in the diagnosis of the disease is much needed. It is the purpose of this article to discuss the symptoms and signs, introducing as far as is pertinent statistics obtained from cases proved by necropsy.

MATERIAL

The data have been obtained from various sources. A group of 61 clinical cases³ and another of 54 necropsies,¹ both at the Massachusetts General Hospital, have been reported. A new series of 24 necropsies at the Boston City Hospital has been added. The analysis of this latter series was made particularly for this article. For this reason certain of the statistics can be drawn from the final group only, whereas

TABLE I
MATERIAL

| Cases | | 78 |
|---|---------------|---------------|
| Lesions, advanced | 67.9 per cent | |
| Lesions, moderate | 26.6 per cent | |
| Lesions, slight | 5.1 per cent | |
| Average age | | 47.9 years |
| Males | | 82.1 per cent |
| Females | | 17.9 per cent |
| Associated with nonsyphilitic heart disease | | 43.6 per cent |

*From the Evans Memorial and Boston University, School of Medicine.

others are obtainable from the entire series of 78 necropsies. The literature on the subject has been utilized* and in addition an unknown number of cases personally examined in hospital and private practice.

Age and Stage.—The average age in the 78 necropsy cases was 47.9 years. The lesions were advanced† in 53 with an average age of 52.5 years, moderate in 21 with an average age at death of 49.6 years, and slight in 4, whose average age was 37.7 years. The minimal age was thirty-one, eighteen, and twenty-one years, in the advanced, moderate, and slight groups, respectively. But 15 of the 78 necropsy cases achieved the age of sixty years; only two passed the age of seventy. In one of the latter the syphilitic lesions were slight and in the other moderate in degree.

Sex.—There were but 14 women in the 78 cases coming to necropsy.

Association With Other Cardiac Diseases.—These 78 necropsies of patients with cardiovascular syphilis showed additional lesions of non-syphilitic origin in 34 (43.6 per cent) of the cases. The data obtained from the final group of 24 necropsies are given in Table I. The combination of other forms of heart disease with that due to syphilis is doubtless well known. It has been pointed out⁴ that its presence should always be suspected in cardiovascular disease, as antisiphilitic therapy may sometimes transform the clinical picture in a favorable direction.

SYMPTOMS

Cardiovascular syphilis often exists in the absence of symptoms. It has been said that the disease is often symptomless until complications such as aortic insufficiency or aneurysm, are present. In the out-patient group substernal pain or shortness of breath was present in all, but in about one-quarter of the necropsy cases there were no symptoms of the disease. The latter statement is, of course, the more important, as it is not surprising that the diagnosis in the living patient is usually made in patients exhibiting symptoms which draw attention to the disease.

Pain, shortness of breath, cough, hoarseness, and weakness are the more prominent symptoms. In many cases the symptomatology is simply that of congestive failure of the heart, or broken compensation if the older term is preferred. These symptoms will bear individual presentation.

Pain.—If there are symptoms, pain is prominent. It varies from an ill-defined pain in the chest, or epigastrium, or a sensation of tightness or burning about the upper sternum to the utter torture of severe angina pectoris. It may come in attacks, be associated with exertion, or be

*More fully in reference 1.

†The lesions were deemed to be slight when but a few plaques were present, moderate when there were many plaques or the latter were large, and severe when the aorta was extensively involved or aortic insufficiency or an aneurysm or both were present.

present almost continuously. In location and radiation the pain sometimes resembles that of angina pectoris.

Pain was present in 28 per cent of the necropsy cases; it conformed to the syndrome of angina pectoris in but 4 per cent. Levine⁶ attributed to syphilis but 7 per cent of a series of cases of angina pectoris. It is probable that the frequency of syphilis as a cause of angina pectoris has been overstressed. I would not, however, belittle the importance of syphilis as a cause of some cases of the anginal syndrome, since recognition of this etiological factor leads to therapy that is often very effective in relief of the patient from this dread affliction.

It is known that syphilis of the aorta may involve the orifices of the coronary arteries, and it is sometimes stated that this localization of the aortic lesions may account for the occurrence of angina pectoris. In our series of 78 necropsies the orifices of the coronaries were narrowed in ten cases. The right orifice was completely occluded in three instances, the left in one, and both in one. Pain, however, was recorded in but two of the patients, in each of whom the necropsy disclosed a narrowing but not complete occlusion of the orifice of the right coronary vessel. The pain did not conform to the syndrome of angina pectoris.

The relation of the pain to the condition of the coronary arteries, aside from their orifices, was carefully analyzed in the final group of 24 necropsies. In 14 cases the coronaries were normal and in 6 of these pain was present; in one it was described as a sensation of pressure, in one that of angina pectoris, and in the other 4 it was a definite pain which did not conform to the syndrome of angina pectoris. In another 6 cases there was slight to marked sclerosis of the coronary arteries but pain was absent. In the remaining 4 with slight to marked coronary lesions pain was present. It is evident that the condition of the coronary arteries was not the determining factor in the presence of the pain.

TABLE II

ASSOCIATION WITH OTHER CARDIAC DISEASE; TWENTY-FOUR NECROPSIES

| | | |
|---|----|-----|
| Arteriosclerosis | | 6 |
| Hypertensive heart disease | | 3 |
| Bacterial heart disease | | 3 |
| Rheumatic heart disease | | 4 |
| Definite | 2 | |
| Probable | -1 | |
| Combined | 1 | |
| Terminal endocarditis | | 1 |
| Congenital heart disease and arteriosclerosis | | 1 |
| Rheumatic heart disease, arteriosclerosis, and hypertensive heart disease | | 1 |
| Total | | 17* |
| No other cardiac disease | | 7 |

*Two cases are entered under two headings; hence the total is 17 not 19.

Further analysis disclosed that the symptom of pain was not related to the degree of syphilitic change in the aorta. In the 78 necropsies

sies there were 18 aneurysms, which gives a percentage of 23. Eleven or over half, were without pain. Fourteen of the aneurysms involved the ascending or transverse part of the arch of the aorta. The fifteenth was a small aneurysm of the descending thoracic arch. The remaining three were below the diaphragm, one each located in the abdominal aorta, the celiac axis, and the superior mesenteric artery.

Shortness of Breath.—This is a common symptom but often is not present until a few weeks or months before death. It appears to be a symptom of congestive failure of the heart and is often associated with edema of the extremities. It was noted in all but 3 of the final group of 24 necropsies. In 2 of these it was characterized as nocturnal dyspnea.

The duration of the shortness of breath in these 21 patients before entrance to the hospital was: three months or less in 4; four to eight months in 6; nine months to two years in 4; few years in 2; and unknown in 5 patients, respectively. All died after relatively short periods in the hospital. This discloses that in 10 cases, or nearly half of those affected by shortness of breath, this complaint had been present not more than eight months before their admission to the wards, and death usually followed within one to two months more.

Cough.—Only 9 of the 24 had cough, and in but 2 of these was it severe.

Weakness.—Two patients complained of weakness. It is reasonable to assume that it was present in many toward the terminal stage but was overshadowed by the other symptoms.

Hoarseness.—This symptom was noted in but one of the 24 cases. In this patient there was an aneurysm of the arch of the aorta. Hoarseness or brassy cough was not noted in 6 other patients in whom an aneurysm of the transverse portion of the aortic arch was found at necropsy.

Dysphagia may be present when an aneurysmal change in the aorta, especially the descending thoracic portion, presses upon the esophagus. It did not occur in this series.

Fever.—An irregular fever has been reported in the literature. It is of exceptional occurrence; fever was not present in any of the 78 necropsy cases that could not readily be explained by other conditions found at the post-mortem examination. I am not aware that I have ever noted it in a patient affected by cardiovascular syphilis.

Duration of the Symptoms.—The relatively short duration of the symptoms before the death of the patient is impressive. In 15 of the 24 necropsies it averaged but eight and one-half months; the extremes were three weeks and two years. In six it was unknown, in the remaining three it was recorded as months, a long time, and years, re-

spectively. (Emerson, in a statistical study,⁶ notes that death usually followed within two years after the development of the disabling symptoms.)

In the clinical group³ the average duration of the symptoms before reporting for treatment was one and one-quarter years. Twelve died; 7 who received mercury and potassium iodide averaged 1.3 years under treatment, and 5 treated chiefly with arsphenamine survived an average of 3.07 years. Ten were alive at the time of the analysis; 9 of these received arsenical therapy. Six of the latter were free of symptoms and able to work. The remainder could not be traced. The conclusion was drawn from these clinical cases that cardiovascular syphilis is a progressive disease but can sometimes be checked by adequate therapy. This opinion finds confirmation in the literature.

Manner of Death.—Patients with cardiovascular syphilis commonly die from progressive failure of the heart. In the final group of 24 necropsies 19 died of congestive heart failure; three of these died suddenly and a fourth while in sleep.

TABLE III
SYMPTOMS

| | |
|--|---------------|
| Absent | 25.0 per cent |
| Pain | 28.0 per cent |
| Angina pectoris | 4.0 per cent |
| Involvement of mouths of coronary arteries | 12.0 per cent |
| With angina† | 0 per cent |
| With non-anginal pain† | 20.0 per cent |
| Coronaries normal* | 58.3 per cent |
| Pain present† | 42.8 per cent |
| Angina pectoris† | 7.1 per cent |
| Coronaries sclerosed* | 41.7 per cent |
| Pain present† | 40.0 per cent |
| Aneurysm of aorta | 23.0 per cent |
| Pain present† | 38.8 per cent |
| Shortness of breath* | 87.5 per cent |
| Nocturnal dyspnea† | 9.5 per cent |
| Cough* | 37.5 per cent |
| Weakness* | 48.3 per cent |
| Hoarseness* | 4.1 per cent |
| Dysphagia | 0 |
| Fever | 0 |
| Duration of symptoms* | 8.5 months |
| Manner of death | |
| From congestive failure* | 79.1 per cent |
| Sudden* | 12.5 per cent |

*Percentage applies only to final group of 24 necropsies.

†Percentage applies to topic below which this item is indebted.

PHYSICAL SIGNS

The evidence of cardiovascular syphilis detected by physical examination varies according to the nature and extent of the lesions present. In many cases, before the condition has become advanced, physical examination discloses no significant abnormal signs.

Cardiac Enlargement.—The heart may be enlarged, but, as is well known, this is not always detected with accuracy by physical examination. The average weight of the heart in the series of twenty-four necropsies was 555 grams (the normal weight of an adult heart varies from 240 to 360 grams⁷). In twelve cases with an average weight of 554 grams the enlargement was detected, but in the remaining twelve with an average weight of 557 gm. the increase in weight of the organ was not disclosed by physical examination. This result is but confirmation of the fact noted above, that hypertrophy of the heart is not accurately detected by physical examination.

Supracardiac Findings.—Percussion over the great vessels, a part of the physical examination that is too frequently neglected, often discloses an abnormal area of dullness. The supracardiac dullness is most marked in the midmanubrial region and in contrast to that found in arteriosclerosis tends to extend farther to the right than the left. Simple dilatation of the ascending aorta, aneurysm, and nonsyphilitic changes must be differentiated.⁸ This datum was not recorded sufficiently frequently in the necropsy series to warrant statistical analysis.

Visible throbbing of the carotids and in the suprasternal notch was present in all but 5 of the 16 cases showing insufficiency of the aortic valve.

A friction sound over the base of the heart was not observed in this series. This finding is of exceptional occurrence; I can recall its detection in but a few cases. It has been explained as due to a plastic exudate on the outer surface of the aorta, but such exudate is rarely found. Perhaps it may be present in association with certain aneurysms of the first part of the aorta.

Murmurs.—A systolic murmur was noted in 18 out of the group of 24 necropsies. It was audible over the preeordia in 12, at the base in 3, at the apex in 3, and was transmitted to the neck in 3. The systolic murmur varies from faint and soft to loud and rough. Occasionally the systolic murmur at the base is accompanied by a thrill, which does not, however, indicate actual stenosis of the aortic valve.

It is well known, of course, that a systolic murmur is present in many hearts that are not affected by syphilitic or any other type of cardiac disease. When these systolic murmurs are attributed to the presence of cardiovascular lues, that at the apex is believed to be due to relative insufficiency of the mitral valve, i.e., the valvular cusps are normal but the ring of supporting muscle has dilated with the dilatation of the left ventricle so that the mitral valve does not completely close.

The aortic valve was normal in 11 of the group of 24 necropsies, but in 6 of these a systolic murmur had been present over the base of the heart. The remaining 13 cases showed some structural lesion of the valve, but in three no basal murmur was detected in life. In 4 of the 10 cases with alteration of the aortic valve and a basal murmur the valve showed

changes (such as a congenital malformation, stenosis of nonsyphilitic origin, etc.) other than mere roughening to account for the murmur. Study of these cases to determine if the basal murmur could be related to roughness of the aortic valve disclosed that such relation was very dubious.

Much attention has been directed to the systolic murmur at the base. This murmur is commonly attributed to roughening of the aortic valve but this explanation is erroneous, since it has been shown elsewhere⁹ that the factor of roughness alone has little if any influence in the causation of a murmur. The more reasonable explanation is that the dilatation of the first part of the aorta, which is common in cardiovascular syphilis, causes the blood ejected through the aortic valve to form a *veine fluide* or jet. The production of a jet in the circulatory system is the most important condition causing a murmur. The physical conditions present when the vessel is dilated just beyond the unnnarrowed aortic valve are identical in their effect on the column of blood ejected to those present when actual stenosis exists; both cause the *veine fluide* or jet and this the murmur. A murmur so produced is commonly transmitted best in the direction of the blood stream. My own experience in examining patients affected by cardiovascular syphilis leads me to believe that the systolic murmur at the aortic area is more frequently transmitted to or toward the neck than was recorded in the necropsy group analyzed in this report.

The diastolic murmur of aortic insufficiency is common. It was noted in 37, or 47.4 per cent, of the 78 necropsies. This murmur is of maximal audibility along the left sternal margin at the third and fourth costal cartilage, or over the second right costal cartilage. It may be audible over the entire precordia, or at times it fades away between the sternum and apex where it may again reappear, especially external to the apex. The diastolic murmur of aortic insufficiency was detected in 16 of the final group of 24 necropsies. Its point of maximal audibility was equally divided between the aortic area (second right costal cartilage) and the left sternal margin. It was transmitted to the apex in 8 cases, and to the neck in but one.

The diastolic murmur of aortic insufficiency, often present in cardiovascular syphilis, begins with the second heart sound and continues a variable period after it. In this respect it differs from the only other common murmur occurring in diastole, i.e., that of mitral stenosis; the latter never begins until just after the second sound.¹⁰ This is in accord with the physiology of the heart since the mitral valve does not open to permit the blood to move through the mitral valve from the left auricle until just after the second sound. It is my impression that too little use is made of noting the exact time when the diastolic murmur begins. The aortic diastolic is also steadier or less rolling in quality, higher pitched, and often louder than that due to mitral stenosis.

It is generally true that diastolic murmurs do not tend to appear and disappear as do many murmurs associated with systole. However, in early cases I have noted, as pointed out by Allbutt,¹¹ that there may for a time be a remarkable intermittency in the murmur; later it becomes permanent.

The diastolic murmur of aortic insufficiency is sometimes audible only if the auscultation is painstakingly performed. The most favorable time is immediately following full expiration and with the patient in the erect or leaning forward posture, as was emphasized by Pardee.¹² Sometimes exercise may intensify the murmur. It occasionally happens that those who do not use the large diaphragm chest-piece of the Bowles stethoscope will detect the aortic diastolic murmur only by listening with the ear applied directly to the chest.

The relation of the diastolic murmur to the lesions of the aortic valve disclosed at necropsy is of interest. An aortic diastolic murmur was detected, as stated above, in 37 of the 78 cases herein analyzed, which gives a percentage of 47.4. The base of the aortic cusps was adherent to the contiguous part of the wall of the aorta in 9 cases, but insufficiency of the valve was demonstrable post-mortem in but 4 of these, though it was manifest in 20 other necropsies without this type of lesion. Aortic insufficiency was present clinically in all 9 of the cases with adherent cusps and in 28 others. Thus, in this series post-mortem evidence of aortic insufficiency was demonstrable in but two-thirds of the cases in which it was noted in life, and in approximately three-fourths of the cases the lesions of the cusps were not the cause of the insufficiency of the valve. Therefore, it seems reasonable to conclude that in most cases the regurgitation is mainly due to yielding of the surrounding muscle and dilatation of the aortic ring.

It is of interest that in a series of 10 necropsies, Juster and Pardee¹³ found involvement of the coronary orifices in each of the 4 cases that showed aortic insufficiency, and not in the remaining 6 without the valvular insufficiency. That this combination is not constant is evident from the fact that in the series of necropsies herein analyzed there were 37 cases in which aortic insufficiency was recognized clinically, 24 in which it was evident at the necropsy, and but 10 in which there was involvement of the coronary orifices. My notes are not sufficiently complete to answer the question of whether the coronary openings ever are narrowed in the absence of aortic insufficiency, but I suspect that such may at times occur.

Austin Flint Findings at the Apex.—In well-marked cases of aortic insufficiency there are sometimes auscultatory findings at the apex which simulate those found in organic stenosis of the mitral valve. It is impossible to analyze their frequency from the data recorded in this series of cases. My personal experience in examining similar cases gives

ground for the opinion that the Flint findings are occasionally present with high grade aortic regurgitation.

Aortic Second Sound.—In the latter group of 24 necropsies there are 6 of the 16 showing aortic insufficiency in which the record contains definite statements in regard to the aortic second sound. In two of these six the aortic second sound was recorded as accentuated and the valve was normal at necropsy; in three it was masked by the murmur, and there were lesions involving the cusps. In the sixth case the aortic second sound was normal and the cusps were thickened, more so, in fact, than in one in which the sound was masked. This confirms the opinion that the second sound sometimes is present in spite of the insufficiency of the aortic valve. In 5 of the 24 necropsies the accentuation of the aortic second sound was noted, and as already stated, in two it was associated with the diastolic murmur of regurgitation.

Allbutt¹¹ emphasized a change in the quality of the second sound, the detection of which he believed to be of value in the diagnosis of syphilitic disease of the aorta. He describes it as a "tympanic second sound" and cites Potain's comparison of it to the sound of the tabourka, an Algerian drum made of an earthen pot with a skin stretched over its mouth. I am satisfied that I have at times detected such a quality in the second aortic sound, but so similar a sound may be heard in arteriosclerosis that, on the basis of the sound alone, I would not have the confidence to diagnose which of these conditions was present. It is probable that the changes in the wall of the aorta when affected by either syphilis or arteriosclerosis are sufficiently alike to have a similar physical effect on the sound produced when the aortic wall is set in vibration. When this tympanic quality of the aortic second sound is considered with all the other evidence, it may be possible to correlate it to cardiovascular syphilis or arteriosclerosis, as the case may be. This physical sign appears to be one of the minor findings and should be used circumspectly until one has acquired sufficient experience in diagnoses confirmed by necropsies, to use it successfully; probably but few have had this experience.

Corrigan Pulse.—The collapsing or water-hammer pulse was present in 11 of the 16 cases of aortic insufficiency in the final series. This vascular phenomenon was described as slight in one case, in three as moderate, and marked in the remaining seven. Its absence in the record of almost one-third of the 6 cases of aortic insufficiency is worthy of emphasis; Stewart¹⁴ reported its absence in 48 per cent of 50 cases. In my experience many physicians are not aware of the fact that the Corrigan type of pulse is not always present in cases of aortic insufficiency. The presence of the Corrigan pulse in these cases could not be closely related to the presence or absence of lesions of the aortic cusps.

Blood Pressure.—Contrary to the belief of some there is nothing characteristic of the blood pressure in cardiovascular syphilis, unless aortic insufficiency is present when the Corrigan pulse is often but not always found. The essential feature of this appears to be a big pulse pressure, i.e., difference between the systolic and diastolic pressure levels, and usually a diastolic pressure lower than the expected normal. The extremes of the pulse pressure with the Corrigan pulse were 70 and 149 mm. Hg.; in its absence the extremes were 30 and 85. In one case in which the Corrigan pulse was noted, the diastolic pressure was 90 mm. The systolic pressure level varied from 130 to 200 mm. with the Corrigan pulse, and 114 to 235 without it. The diastolic pressure averaged 67 mm. with and 69 mm. without the Corrigan pulse. Except for the changes in the blood pressure levels associated with insufficiency of the aortic valve, it was impossible to relate the instances of elevated pressure of the blood to the presence of cardiovascular syphilis; the presence of chronic arterial hypertension could not be excluded.

Development of the Physical Signs.—May I quote from a previous paper?¹⁵ "My first study of a series³ of cases of cardiovascular syphilis, in which I either examined the patients or had their medical records covering frequently a period of years, has stamped indelibly on my mind the progressive nature of this disease. Case after case first showed nothing abnormal in the cardiac findings, later a systolic murmur appeared at the aortic area, and after a period of a few months to about a year, the murmur of aortic regurgitation and often that of a mitral leak and advanced heart failure developed."

Noncardiac Signs of Syphilis.—If the physical examination is conducted with sufficient care and is complete, it is not uncommon to find evidence suggestive of syphilis. Changes in the pupils, enlargement of the epitrochlear glands, alterations in the tongue, a scar on the prepuce, anal condylomata, certain scars on the skin, sabre-shaped tibiae, altered reflexes, etc., may suggest syphilis. It is noteworthy that changes in the pupils were frequent in the series of 24 necropsies. In 7 the pupils were irregular; in 6 they were unequal; in 5 the reaction to light was sluggish; and in 3 the pupil was of the Argyll-Robertson type. The pupils were normal in but 10 of the 24 cases.

WASSERMANN REACTION

The Wassermann reaction on the blood was obtained in 42 of the necropsies. In 25 it was positive, in 7 suspicious or moderately positive, and in 10 it was negative. In percentages the figures are: 59.5 per cent, 16.6 per cent, and 23.8 per cent, respectively. The percentage of positive reactions is lower than is found in much of the literature. Twenty-three per cent of negative Wassermann reactions need cause little surprise when it is recalled that this reaction is not positive at all times in cases of proved syphilis. The difficulty is that there is too

often a tendency to doubt the diagnosis of cardiovascular syphilis because the Wassermann reaction is negative. A positive reaction supports the diagnosis, but if negative the diagnosis should remain unshaken if indicated by other evidence.

As in other conditions due to syphilis the history of having had this infection is often negative. Nine of the patients in the series of 24 necropsies admitted a chancre; an average of 25 years had elapsed since the occurrence of the chancre.

The question is sometimes raised if it is not desirable to do a lumbar puncture and obtain a Wassermann test on the spinal fluid in those cases in which the test is negative on the blood. In my opinion such a procedure is both unnecessary and places too much importance upon the Wassermann reaction. As stated above, a diagnosis of cardiovascular syphilis should not be abandoned merely because the Wassermann reaction on the blood is negative. If the data as a whole indicate the presence of cardiovascular syphilis, treatment should be administered at least to the extent of an adequate therapeutic test. If a positive reaction were obtained on the spinal fluid, this does not, of course, prove the presence of cardiovascular syphilis; syphilis of the central nervous system may be present. The diagnosis of cerebrospinal syphilis is not germane to this article.

It need hardly be said that the Kahn or Hinton modifications of the Wassermann reaction should be made use of; they will probably give a somewhat higher percentage of positive reactions if syphilis is present.

ROENTGEN RAY FINDINGS

Roentgen ray examination offers further data of value in diagnosis. It is, however, inconsistent with our knowledge of the pathology of cardiovascular syphilis to believe that in early cases evidence of its presence can be disclosed by the x-ray. How can one expect that some perivascular infiltration or a few plaques in the aortic wall can be detected by the roentgen ray? In sufficiently advanced cases, however, roentgen ray examination is very helpful, often giving the first definite evidence of the presence of cardiovascular syphilis. The radiologist failed, nevertheless, to make the correct diagnosis in five cases in this series in which the lesions were advanced. When one is familiar with the complexity of the differential diagnosis, these failures need cause no surprise.

The details of the roentgen ray findings have been well described by Holmes¹⁶ and others and will not be repeated here.

ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram, in my experience, does not show changes indicative of cardiovascular syphilis. The electrocardiograms taken on 50 cases¹⁷ of early syphilis were essentially normal. Nothing distinctive

was found in the tracings taken in 34 patients¹⁸ clinically diagnosed to have syphilitic heart disease. However, a recent study¹³ of 50 patients with cardiovascular syphilis disclosed the following: the T-wave was abnormal in 85 per cent of the 16 patients having aortic insufficiency and in 20 per cent of these the T-wave was of the coronary type. In the 34 patients without the aortic leak the T-wave was abnormal in but 38 per cent, and only one case (7 per cent) showed a wave of the coronary type. The prognosis was much more unfavorable in the patients with the abnormal T-waves.

TABLE IV

SIGNS

| | |
|--|---------------|
| Average weight of heart* | 555 grams |
| Enlarged heart* | 91.6 per cent |
| Aortic insufficiency* | |
| Present† | 66.6 per cent |
| Absent† | 33.3 per cent |
| Systolic murmur* | 75.0 per cent |
| Diastolic murmur | 47.4 per cent |
| Aortic cusps adherent to aortic wall† | 24.3 per cent |
| Diastolic murmur* | 66.6 per cent |
| Transmitted to apex† | 50.0 per cent |
| Transmitted toward neck† | 6.2 per cent |
| Aortic second sound* | |
| Accentuated | 20.8 per cent |
| With aortic insufficiency | |
| Accentuated | 12.5 per cent |
| Masked | 12.5 per cent |
| Unmentioned | 75.0 per cent |
| Corrigan pulse, with aortic insufficiency* | |
| Present | 68.7 per cent |
| Absent | 31.3 per cent |
| Pupils | |
| Abnormal | 58.7 per cent |
| Irregular | 29.2 per cent |
| Unequal | 25.0 per cent |
| Sluggish | 20.8 per cent |
| Argyll-Robertson | 12.5 per cent |
| Wassermann reaction | 42 cases |
| Positive† | 59.5 per cent |
| Suspicious† | 16.6 per cent |
| Negative† | 23.8 per cent |

*Percentage applies only to final group of 24 necropsies.

†Percentage applies to topic below which this item is indented.

In my opinion it seems best to consider abnormalities in the electrocardiogram to be indicative of the presence of cardiac disease, but not of the etiology of the latter. Thus, one finds electrocardiograms depicting various degrees of heart-block, bundle-branch block, auricular fibrillation, etc., in cases proved by necropsy to have cardiovascular syphilis, but the diagnosis of syphilis as the causative factor cannot be determined from the electrocardiographic findings. When these latter are correlated to the data obtained by the other methods of clinical and laboratory examination, they may be decided to be of luetic origin and contribute much to the understanding of the case.

DISCUSSION

The presence of cardiovascular syphilis was diagnosed clinically in 43 of the entire series of 78 necropsies; in 35 it was not. In 12 of the latter the lesions were of an advanced degree. There was, then, a failure to diagnose the disease in 44 per cent, and in 34 per cent of these failures the condition was in an advanced state.

The first essential in the diagnosis of cardiovascular syphilis is that it be considered as one of the possible diagnoses in any adult in whom cardiac disease is deemed to be present. The more or less recent recognition of the necessity of determining the type of heart disease, i.e., rheumatic, hypertensive, syphilitic, etc., is proving of value in the detection of those cases in which cardiovascular syphilis exists. The modern clinician is no longer satisfied with the diagnosis of myocarditis as a complete statement of the condition that may be present; some of these are instances of cardiovascular syphilis in which the myocardial changes are but one feature.

Every case affected by syphilis is one of potential heart disease.¹⁹ The term potential heart disease is applicable here as it is in those who have had one of the rheumatic group of infections, such as rheumatic fever, chorea, or tonsillitis. The interval between the primary stage of syphilis and the onset of clinical disease of the heart and aorta is, of course, much longer than that usually elapsing in the case of rheumatic heart disease.

DIFFERENTIAL DIAGNOSIS

The presence of cardiovascular syphilis is the more probable if other conditions can be excluded as the cause of the abnormal symptoms and signs pertaining to the circulation. Such conditions as nonspecific aortitis, arteriosclerosis of senescence, hypertensive heart disease, rheumatic heart disease, pulmonary tuberculosis, mediastinal tumors, and perhaps some cases of tabes dorsalis are among the more significant diseases from which cardiovascular syphilis must be differentiated. The details of differential diagnosis have been sufficiently discussed elsewhere.^{1, 8, 16, 20}

SUMMARY

The symptoms and signs of cardiovascular syphilis are discussed. An analysis was made of 61 clinical cases and 78 necropsies; statistics limited to the cases proved post-mortem are presented.

The average age at death was 47.9 years. There were but 3 cases under thirty years of age, and only 2 above seventy years.

Males outnumbered the females in the ratio of 5.5 to 1.

The syphilitic lesions were associated with lesions of nonsyphilitic disease of the heart in 43 per cent of the necropsies.

Symptoms of the disease were absent in about one-quarter of the patients in whom the disease was disclosed at necropsy.

Pain was present in 28 per cent. It conformed to the syndrome of angina pectoris in but 4 per cent.

The mouths of the coronary arteries were partially occluded in 10 patients; none of these had angina pectoris, and 8 were without pain of any sort.

Neither the presence nor the character of the pain could be related to the condition of the coronary arteries or of the aorta.

The coronary arteries were normal in 58.3 per cent of the series of 24 necropsies.

Shortness of breath was common after the onset of congestive failure of the heart.

The symptoms of weakness, hoarseness, dysphagia, and fever were absent or were present in a negligible number of these patients. Hoarseness of the voice was noted in but one of seven cases of aneurysm involving the transverse portion of the aortic arch.

The duration of the symptoms rarely exceeded a few months in the necropsy cases; it was somewhat longer in the clinical series treated as out-patients. From these latter there is presumptive evidence that adequate therapy may relieve symptoms and prolong life.

The manner of death was that of progressive failure of the heart in 79 per cent of the series of 24 necropsies. In 4 of these the actual death was sudden.

The heart was enlarged in 22 cases, or 91.6 per cent, of the 24 necropsies. This enlargement was present in the absence of aortic insufficiency in 7, or about one-third of the group. The average weight of the heart was 555 gm.

Increase in the supracardiac dulness and other findings above the heart are common, but too often not recorded in the physical examination.

A systolic murmur over the precordia or more localized at the apex or base is common. That at the base is not due to roughening of the

The diastolic murmur of aortic insufficiency was noted in 47.4 per cent. In 50 per cent of the 16 aortic regurgitant cases in the series of 24 necropsies the diastolic murmur was transmitted to the apex. aortic valve.

This diastolic murmur may be inconstant in its presence in its earlier stages. Its detection sometimes requires painstaking auscultation.

Aortic insufficiency was recognizable in half again as many cases as were evident at post-mortem, and in at least three-fourths of the cases (murmur present in life) the regurgitation could not be attributed to lesions of the valve. The insufficiency of the valve is best explained as due to yielding of the muscular ring round the aortic orifice.

The apical findings, known as those of Austin Flint, are occasionally present.

The aortic second sound may be masked by the murmur of aortic insufficiency, or it may be accentuated in the absence of the murmur and even if the latter is present.

A change in the quality (i.e., a tympanic note) may take place in the aortic second sound, but it is difficult to differentiate from that found in arteriosclerosis of nonsyphilitic causation.

The Corrigan type of pulse was absent in 5 of 16 cases of aortic insufficiency. That such is possible does not appear to be generally recognized.

There is nothing characteristic of the blood pressure save in the presence of aortic insufficiency.

Careful physical examination may detect evidence suggestive of syphilis elsewhere in the body.

The Wassermann reaction was negative in 10, or 23.87 per cent, of the 42 cases in which it was recorded.

The roentgen ray findings are very important aids in the diagnosis. It is unreasonable, however, to expect that the slight lesions in early cases of cardiovascular syphilis can be detected by the roentgen ray. In advanced cases the differential diagnosis from nonsyphilitic conditions may be difficult or impossible solely from the roentgen ray findings.

The presence of cardiovascular syphilis was not diagnosed in 44 per cent of this series, although the subsequent necropsy disclosed advanced lesions in one-third of these failures.

About one in five of the cases in which the syphilitic lesions were of advanced degree remained undiagnosed in life.

REFERENCES

1. Reid, W. D.: Specific Aortitis, Boston M. & S. J., 183: 67, 105, 1920.
2. Idem: Review of the Heart Findings in the Medical Autopsies at the Boston City Hospital During 1921, Med. Rev. of Rev., 445, 1923.
3. Idem: Prognosis of Specific Aortitis, J. A. M. A., 73: 1832, 1919.
4. Minet, J., Dubot, E., and Legrand, R.: Syphilis Plus Febrile Rheumatism, Paris méd., 2: 389, 1921.
5. Levine, S. A.: Angina Pectoris. Some Clinical Considerations, J. A. M. A., 79: 928, 1922.
6. Emerson, H.: Economic Aspects of Heart Disease, AM. HEART J., 4: 258, 1929.
7. Gray, H.: Anatomy, Descriptive and Applied, Philadelphia, 1913, p. 562, Lea and Febiger.
8. Reid, W. D.: The Heart in Modern Practice, Philadelphia, Ed. 2, p. 36, J. B. Lippincott Co.
9. Idem: The Production of Heart Murmurs, Am. J. M. Sc., 165: 329, 1923.
10. Idem: The Heart in Modern Practice, Philadelphia, Ed. 2, p. 99, J. B. Lippincott Co.
11. Allbutt, C.: Diseases of the Arteries, Including Angina Pectoris, New York, 1915, vol. II, p. 140, The Macmillan Co.
12. Pardee, H. E. B.: The Murmurs of Mitral Stenosis and of Aortic Regurgitation, Am. J. M. Sc., 158: 319, 1919.

13. Juster, I. R., and Pardee, H. E. B.: Abnormal Electrocardiograms in Patients with Syphilitic Aortitis, *AM. HEART J.*, 5: 89, 1929.
14. Stewart, H. E.: Experimental and Clinical Investigation of the Pulse and Blood Pressure in Aortic Insufficiency, *Arch. Int. Med.*, 1: 102, 1908.
15. Reid, W. D.: The Diagnosis of Cardiovascular Syphilis, *Boston M. & S. J.*, 188: 189, 1923.
16. Ledbetter, P. V., Holmes, G. W., and White, P. D.: Value of X-Ray in Determining Cause of Aortic Regurgitation, *AM. HEART J.*, 1: 196, 1925.
17. Turner, K. B., and White, P. D.: The Heart and Aorta in Early Syphilis, *Arch. Int. Med.*, 39: 1, 1927.
18. Smith, D. C., and Kimbrough, R. D.: Syphilitic Heart Disease With Failure, *South. M. J.*, 21: 634, 1928.
19. Reid, W. D.: The Prevention of Cardiovascular Syphilis, *Am. J. Syphilis*, 8: 609, 1924.
20. Idem: The Differential Diagnosis of Cardiovascular Syphilis, *Am. J. Syph.*, 14: 188, 1930.

DISCUSSION

Dr. Alexander Lambert, New York, N. Y.—I would like to ask Dr. Reid to explain his differentiation of pain of the coronary type and the noncoronary type in syphilitic disease. Pain in coronary disease is known to be three and one-half times as frequent in the hypochondria and epigastrium as in the chest and down the left arm.

Dr. Wm. D. Reid (closing).—If I understood Dr. Lambert rightly he asked for more details as to how we separate pain called angina pectoris from the other group. There is a large degree of the personal equation of whoever answers this question; classifications of angina differ considerably. Angina pectoris is closely related to exertion and is relieved by nitroglycerin. The pain is of short duration and has a typical radiation. In the other group the pain is not particularly under the sternum, is not related to exertion, and is of longer duration. A woman can do her housework all day without pain and have the pain at night. When the Wassermann reaction is negative, it does not mean that the cardiac condition is not due to syphilis. Dr. Hinton, of Boston, is working on a modification of the blood Wassermann which will be much more specific, and it is hoped make it unnecessary to test the spinal fluid. However, we must not rely so much on the Wassermann as on the general picture.

THE DIFFERENTIATION OF SYPHILITIC FROM FUNCTIONAL AND OTHER FORMS OF AORTIC INSUFFICIENCY*

LESLIE T. GAGER, M.D.

WASHINGTON, D. C.

IN THE degree that a disease is endemic, its diagnosis is likely to become deceptively easy. Where acute rheumatic fever prevails as the chief cause of heart disease, as in New York and New England, it is natural, in relation to aortic insufficiency, to think first of this etiologic agent. In Washington¹⁰ and further south, as syphilis, especially in the negro,¹⁶ comes to equal and surpass other infections in producing the cardiovascular lesions of early and middle adult life,† there results a distinct diagnostic leaning toward this disease.

Inferences based on probabilities are often correct: in spite of her age, the diagnosis of syphilitic aortitis was made in a seventeen-year-old negro girl with aortic insufficiency (there was a positive Kahn test and no rheumatic history) and confirmed at necropsy. But in other patients, in whom the diagnosis of syphilitic aortic insufficiency had been made, or seriously considered, this etiology was disproved, and some of these problems of differential diagnosis I wish to discuss and illustrate.

Under the title of true and false aortic insufficiency, Barié,² in 1896, presented an extensive review of the subject, much disputed since Corrigan,⁶ of the differing modes of origin and meaning of diastolic murmurs arising, if not always heard, at the base of the heart; and his classification remains so useful and practical a guide that I have followed it in the accompanying schema. His views, indeed, Barié defended in 1923, when interest in functional aortic insufficiency had been renewed by a series of case reports.^{3, 13, 14}

Of these five groups of possible signs or simulations of aortic insufficiency, the last four, while of much interest, must be rapidly disposed of here.

The diagnosis of aortic insufficiency without the diastolic murmur has not often been made, though frequently in hyperthyroidism and not rarely in hypertension, a high pulse pressure suggests the search for regurgitation. Dumas,⁷ however, has recently reported an example, proved by necropsy, in which the recognition was based on high pulse and differential pressures and loss of the aortic second sound. The clinical observations of Fürbringer, Leyden and Litten are cited by

*From the Department of Medicine, George Washington University School of Medicine.

†Dr. Frank Leech informs me that of 3715 admissions to the Children's Hospital, Washington, D. C., in 1929, there were 46 cases of rheumatic infection and 34 cases of rheumatic heart disease (0.92 per cent). No syphilitic heart disease was found.

Barié, who quotes Leube's opinion that in advanced insufficiency the valvular alterations might be so great as to prevent the vibrations necessary to produce a murmur.

Propagation of the aortic diastolic murmur from base to apex or beyond, or to the region of the xiphoid process, dependent on predominant lesions of the posterior cusps or other factors, has become a familiar observation.

The suspicion of syphilis aroused by an accentuated, bell-like or drum-like aortic second sound (Potain's *bruit de tabourka*) may be heightened when a coincident whiff or short diastolic murmur is audible. But the underlying changes in the root of the aorta need not be syphilitic.¹ These signs, in a hypertensive patient with a history of chancre, aortic dilatation and a positive Wassermann reaction and a temporarily favorable response to the therapeutic trial of a few small doses of neoarsphenamine, were subsequently found to be associated with simple atheromatosis and unchanged valves. Austin Flint² described this "aortic diastolic non-regurgitant murmur," which is characteristically linked with a systolic aortic murmur and is entirely an arterial phenomenon.^{2, 4} But a diastolic murmur may be frankly audible at the base or along the sternum, and its seat of origin be not at all clear, just as its intensity is notoriously independent of extent of lesion or amount of regurgitation.

TABLE I
CLASSIFICATION OF AORTIC INSUFFICIENCY

| | |
|---|---|
| I. With a basal diastolic murmur. | |
| A. True insufficiency. | |
| | 1. Malformation |
| | 2. Trauma |
| Valve lesions due to | 3. Endocarditis |
| | 4. Syphilis |
| | 5. Sclerosis |
| B. Functional (relative) insufficiency. | |
| Dilatation of aortic ring, without valve lesion. | |
| | 1. Dilatation of aorta, e.g., by hypertension. |
| | 2. Dilatation of left ventricle: anemia, failure. |
| | 3. External traction: adherent pericardium. |
| II. With accentuated aortic second sound obscuring a diastolic murmur, or coinciding or alternating with it. | |
| Due to atheromatous, and usually dilated, aorta. | |
| III. With an apical diastolic murmur only (transmitted from aortic area). | |
| IV. With no diastolic murmur audible (peripheral signs only). | |
| V. Pseudoin sufficiency (with a diastolic murmur arising elsewhere than in the aortic area: pulmonic insufficiency [Graham Steele]; septal defect; accidental). | |

A man of twenty-eight years, who has had no intimation of heart disease and who denies both rheumatic and syphilitic infection, though the blood Wassermann test is four plus, has come under observation following an hemoptysis. The lungs are clear. Aortic dulness is not widened, but both to right and left the heart is greatly enlarged. Over the precordium is a long systolic thrill, and a harsh

systolic murmur is loudest in the third and fourth interspaces at the sternal border. In the same area is heard a smooth high-pitched diastolic murmur which is not made out at the base. Blood pressure is 125/60 mm. in both brachial arteries, 160/60 in the femoral. The liver is not enlarged. There is no clubbing or cyanosis of the fingers.

Is this syphilitic aortic insufficiency or a septal defect? In all diameters fluoroscopy shows an undilated aorta. The globular heart measures 17 cm. in transverse diameter, with chest width 26 cm. The electrocardiogram shows no ventricular predominance.

Pulmonic insufficiency is usually set apart by the presence of mitral stenosis and the absence of ventricular hypertrophy and peripheral signs of aortic insufficiency, but Holt¹² has shown the difficulty of differentiation that may arise. In her patient, with a large heart, mitral stenosis and terminal pneumococcus endocarditis, an adherent pericardium was found at necropsy, the same condition which Laubry and Doumer¹³ found associated with dilatation of the left ventricle and relative aortic insufficiency. In such cases, the possibility exists of external traction and deformity of the aortic ring; protrusion of the septal wall into the ventricle with elevation of a cusp has been suggested,⁴ while the important factor of ventricular dilatation in throwing strain on the aortic vestibule and orifice is shown by the following patient:

A negro male, aged forty-one years, was admitted to the hospital with fever and weakness. Eight weeks before admission his tongue had become covered with white patches, a blood Wassermann test was found positive and several intravenous injections were given.

In addition to an intense stomatitis, examination revealed marked carotid pulsations, a greatly enlarged heart and a blowing diastolic murmur to right and left of sternum in the second interspace. The blood pressure was 128/54 mm. The diagnosis seemed obvious until the sudden onset of hemiplegia brought up the question of bacterial endocarditis. The necropsy revealed a normal aorta and intact aortic valves; both ventricles were enormously dilated and on one mitral cusp was a large fresh vegetation. Staphylococci were recovered from the heart's blood.

Goldstein and Boas¹¹ have linked the functional diastolic murmur occurring in severe anemia with the presence of cardiac dilatation, and this has been my observation in two recent cases, while in a man whose hemoglobin, before liver extract was given, had dropped to 9 per cent, there was neither cardiac embarrassment nor murmur.

Inconstancy is frequently a characteristic of the functional basal diastolic murmur. An instance of its modification by change in position of the patient is of interest:

A negro male of about thirty years was admitted with the signs of tuberculous pleurisy with effusion and was tapped. Without central or peripheral evidence of circulatory disease, and a negative Wassermann test, this man showed a distinct diastolic murmur at the base of the heart while in the recumbent position. In the erect position, the murmur disappeared.

How shall such a murmur be explained? Potain noted a soft circumscribed murmur in a tuberculous patient whose aorta and valves were later found normal (cited by Barié). In such patients as these, mediastinal adhesions between aorta and chest wall are not beyond possibility. Barié considered murmurs of this description to be accidental, cardiopulmonic, possibly venous in origin, and often definitely associated with anemia.

Hypertension, both transient and persistent, bears an important causal relation to functional aortic insufficiency. The appearance of a diastolic murmur with an attack of bronchial asthma was noted by Fleckseder⁸; in Vaquez's¹⁹ patient, a man with hypertension and angina pectoris, aortic insufficiency appeared during a severe attack of pain and disappeared with its recession.

Numerous observers^{2, 3, 13, 14, 15, 19} have noted the association of aortic dilatation and relative aortic insufficiency with chronic hypertension or granular kidneys. The salient features of three such examples follow:

A male, aged thirty-two years, was sent to hospital from the heart clinic, because of fatigue and dyspnea, with blood pressure 268/178 mm. He was rather well nourished, only slightly anemic, showed a faint trace of albumin in the urine, and had a negative blood Wassermann reaction. Retinitis appeared; the urea nitrogen increased from 29 mg. to 188 mg. per 100 c.c. of blood, and death occurred in six weeks. There was constantly present a loud blowing diastolic murmur in the second right interspace and down the left border of the sternum. At necropsy, the aortic ring was distinctly dilated, and there was well-marked atheromatosis, but the valves were only slightly thickened.

A man, aged sixty-eight years, with dyspnea and pain of aortic distribution, showed moderate peripheral arteriosclerosis, a rather large heart, some dilatation of the aorta, and a blood pressure of 240/130 mm. There was a booming aortic second sound, and a high pitched murmur occupying most of diastole was heard in the second right interspace, down both sides of the sternum and also outside the apex. Post-mortem study, after rupture of a dissecting aneurysm, showed the aortic orifice dilated, with no valvular disease and only slight sclerotic changes in the intima of the aorta.

A laborer, aged thirty-nine years, recently came under observation complaining of palpitation, breathlessness and cramps in the legs. His blood pressure was 230/150 mm.; aortic and cardiac dulness was increased, and a long basal diastolic murmur was present on both sides of the sternum and transmitted down its left border. There was a history of chancre at twenty-five years, but the blood Wassermann test was negative. While syphilis was not excluded, it was felt that the high diastolic pressure was strong contrary evidence.

Of the less common causes of valvular lesions, fenestrated cusps⁸ and other anomalies¹⁷ may cause insufficiency or aid in dilatation of the ring. Rupture of a cusp following heavy lifting was seen in a young syphilitic negro, with a rough double thrill and murmur at the base. In an ex-prize fighter of thirty-four years, apparently healthy and an applicant for insurance, a fairly harsh aortic diastolic murmur was unexpectedly discovered. Rheumatic and syphilitic infections were denied, and his wife has had four healthy children. Sclerosis of the valves,

without antecedent hypertension, I believe to be rare, in spite of senescent dilatation of the aorta^{5, 18} as an accessory factor.

In summary, in the course of studying aortic insufficiency and diastolic murmurs under conditions, such as race, age, sex and climate, which make syphilis the outstanding etiologic factor, exceptions have been found frequently enough to show a plurality of causes and mechanisms. Not the least interesting finding has been that of relative aortic insufficiency. Differentiation requires avoiding a diagnostic bias and giving attention to the whole clinical picture.

REFERENCES

1. Allbutt: Diseases of the Arteries, 2: 201, London, 1915, The Macmillan Co.
2. Barié: La vraie et les pseudo-insuffisances aortiques. Arch. gén. de Méd. 80 sér., 5: 251, 401, 569, 1896; Discussion. Bull. et mém. Soc. méd. d. hôp. de Paris, 47: 594, 1923.
3. Bergé and Basch: Insuffisance aortique . . . de la dilatation de l'anneau aortique par hypertension. Bull. et mém. Soc. méd. d. hôp. de Paris, 46: 1700, 1922.
4. Bret: Pression artérielle et lésions dans quelques cas d'insuffisance aortique dite fonctionnelle. Arch. d. mal. du cœur, 12: 194, 1919.
5. Boas and Fineberg: Hypertension and Its Relationship to Mitral Stenosis and Aortic Insufficiency. Am. J. M. Sc., 172: 648, 1926.
6. Clendenning: Corrigan's Description of Aortic Insufficiency. Arch. Int. Med., 37: 780, 1926.
7. Dumas and Guillemin: Insuffisance et rétrécissement aortique . . . et absence habituelle de souffle diastolique. Lyon méd., 138: 631, 1926.
8. Fleckseder: Eine seltene Ursache von Insuffizienzgeräuschen an den Aortenklappen. Wien. klin. Wchnschr., 40: 55, 1927.
9. Flint, Austin: Manual of Percussion and Auscultation, Philadelphia, Ed. 3, p. 209, 1883, Lea's Son and Co.
10. Gager: Syphilitic Heart Disease. Am. J. Syph., 13: 411, 1929.
11. Goldstein and Boas: Functional Diastolic Murmurs and Cardiac Enlargement in Severe Anemias. Arch. Int. Med., 39: 226, 1927.
12. Holt: Signs of Aortic Insufficiency in Absence of Aortic Lesion. AM. HEART J., 2: 573, 1927.
13. Laubry and Doumer: Sur l'insuffisance aortique fonctionnelle et sa pathogénie. Bull. et mém. Soc. méd. d. hôp. de Paris, 47: 584, 1923.
14. Lian: Discussion, Ibid, 46: 1704, 1922.
15. Mosenthal: Variations in Blood Pressure, etc., Oxford Monographs on Diagnosis and Treatment, 7: 160, Oxford Univ. Press, 1929.
16. Pandlin: Incidence of Syphilitic Infection in the Negro, etc., Tr. A. Am. Physicians, 42: 46, 1927.
17. Peacock: Valvular Lesions of the Heart, Chapter on Malformations, London, 1865, Churchill and Sons.
18. Perls: Über Weite und Schlussfähigkeit der Herzmündungen und ihre Klappen, Deutsches Arch. f. klin. Med., 5: 381, 1869.
19. Vaquez: Diseases of the Heart, translated by Laidlaw, pp. 454, 318, 377, 378, Philadelphia, 1924, W. B. Saunders Company.

DISCUSSION

Dr. F. N. Wilson, Ann Arbor, Mich.—I should like to point out that the importance of any condition depends upon its frequency. Of the cases of aortic insufficiency that I have seen, 90 per cent or more have been either rheumatic or lentie. I have seen cases of arteriosclerotic aortic insufficiency, but in my experience this condition has been relatively rare. I have never seen a case of free aortic regurgitation, that is aortic regurgitation with pronounced vascular signs, due to this cause. The percentage of all cases of aortic insufficiency due to subacute and acute bacterial endocarditis is relatively small. Congenital aortic insufficiency is very rare.

I have never seen an instance of aortic insufficiency which I could attribute with confidence to functional dilatation of the aortic ring, nor have I ever seen an accidental aortic diastolic murmur. I do not question that both occur, but I believe that they are very rare.

The great majority of the cases of aortic regurgitation in which pronounced vascular signs occur are luetic. Another sign that should lead one to suspect luetic involvement of the aorta is the presence of palpable pulsation when the fingers are placed upon the cricoid cartilage. The heart beat cannot normally be felt at this point. I believe that the change in the aortic second sound which occurs in luetic aortitis differs from that which occurs in hypertension and in arteriosclerosis, and I believe that this difference is due to the dilatation of the first part of the aorta in luetic aortitis. The arteriosclerotic aorta is lengthened rather than dilated, and the quality of the second sound is different.

Dr. Lee, Washington, D. C.—I think *Dr. Wilson's* remarks are well taken. The burden of proof belongs to those who have to show that it is not an organic condition. We do sometimes have functional diastolic murmurs. One old lady had an atheromatous condition with a typical long diastolic murmur after severe fits of coughing, with stress on the circulation which, however, was not present at other times. Sometimes these cases are temporary, sometimes permanent, but they are rare.

Dr. H. S. Feil, Cleveland, Ohio.—Some years ago I studied the subelavian pulse in a large series of aortic cases. Registration was made by means of the optical sphygmographic method of Wiggers. It was found that the pulse in luetic aortic insufficiency was characteristic. When ejection was free, the case was usually luetic, while with evidence of stenosis the pathological lesion was rheumatic or sclerotic.

Dr. Gager (closing).—I do not wish to leave the impression that in the majority of instances the aortic insufficiency of adults which I see in Washington is not syphilitic. But every now and then occur these exceptional cases of aortic insufficiency which, because specific aortitis is common, may be diagnosed as due to syphilis when some other condition is responsible. It is the practical importance, for prognosis and treatment, of keeping in mind and recognizing these various possibilities, as well as the interest of the differential diagnosis, that I would emphasize.

A STUDY OF THE COURSE OF SYPHILITIC CARDIOVASCULAR DISEASE*

FREDRICK A. WILLIAMS, M.D.

ROCHESTER, MINN.

THIS study was undertaken to obtain data relative to the duration of life of patients with cardiovascular syphilis. I have been unable to find definite information regarding this point in the medical literature. Studies of this type are of considerable importance as they permit the substitution of relative quantitative values for uncertain clinical impressions. They may be said to represent the life cycle of disease.

MATERIAL AND METHOD

This investigation comprised 100 men selected from a group of 600 patients with cardiovascular syphilis. Cases were included in the study only if the following factors were present: (1) an accurate history of the time of onset of syphilis, (2) the presence of syphilitic cardiovascular disease, and (3) the exact date of and the mode of death from cardiovascular disease. The strict adherence to these criteria, which was necessary in order to obtain reliable data, account for the relatively small series. The patients were all males. To obtain accurate histories of the time of onset of syphilis in women is difficult. This is partly the result of their reluctance to confess that they know the time of onset and in part to the fact that there are greater possibilities of failure to recognize the existence of a primary syphilitic lesion in a woman than in a man.

The cases were grouped according to the type of lesion as determined by clinical methods of examination. The diagnosis of the type of lesion is presumed to be as accurate as clinical methods will permit. In addition to a complete general examination and routine laboratory investigation the patients were all subjected to roentgenographic study of the heart; electrocardiograms were taken of all, the Wassermann reaction of the blood was determined in all cases, and of all but six, studies of the spinal fluid were made. Detailed neurological investigation was conducted whenever it was thought necessary.

RESULTS

The cases were grouped as follows: (1) syphilitic aortitis, (2) syphilitic aortitis with aortic insufficiency, and (3) thoracic aneurysm.

Syphilitic Aortitis.—Seventeen cases comprised this group. The average age of the patients at the time that syphilis was contracted was

*Read by title from the Section on Cardiology, The Mayo Clinic, Rochester, Minn.

thirty-one years. The earliest age was nineteen years, and the latest age recorded was fifty-three years. The average age at which these patients died of cardiovascular disease was fifty-four years; that is, an average of twenty-three years elapsed from the onset of syphilis to the time of death. Seizures of cardiac pain occurred in three cases and these were the only instances in which sudden death occurred. The Wassermann reactions of the blood were positive in 65 per cent of the cases. Examinations of the spinal fluid were carried out in fourteen cases and in only two the reaction was positive. Syphilis of other systems of the body was demonstrated in 24 per cent of the cases. Important alterations in the electrocardiogram occurred in twelve cases (71 per cent). Significant T-wave negativity occurred in eleven cases. Two instances of auricular fibrillation were observed. The relatively rare association of auricular fibrillation and aortic disease has been emphasized on numerous occasions.

Syphilitic Aortitis With Aortic Insufficiency.—This group comprised fifty-nine cases which uniformly presented advanced cardiovascular involvement. The average age of occurrence of the primary syphilitic lesion in this group was twenty-six years, five years earlier than in Group I; the youngest patient was aged sixteen years and the oldest, forty-nine. Death from cardiovascular disease occurred at the average age of forty-nine years; this is an average period of twenty-three years from the inception of the syphilitic infection. Painful cardiac seizures occurred in fifteen (25 per cent) of the cases, and in eight of these death occurred suddenly. The Wassermann reactions of the blood of 68 per cent of the patients were positive. In fifty-six cases studies of the spinal fluid were made; eleven were positive. Associated syphilitic disease occurred in seventeen cases. Electrocardiographic abnormalities of importance occurred in thirty-seven cases (63 per cent). Significant T-wave negativity, as in Group I, was the predominant graphic characteristic. It occurred in thirty-three cases. There were two cases of complete heart-block, one of delayed auriculo-ventricular conduction, and one of complete right bundle-branch block. Only two cases of auricular fibrillation occurred.

Thoracic Aneurysm.—In twenty-four cases, thoracic aneurysm was present. The aortic arch and ascending aorta were involved in twenty-two cases, whereas there was aneurysm of the descending aorta in two. Patients in this group had contracted syphilis at the average age of twenty-seven years. The earliest age of infection was nineteen years and the latest, forty years. The average age at which death occurred from cardiovascular disease was fifty-three years, twenty-six years after infection. The average period of duration is comparable to those of the other groups. Painful cardiac attacks occurred in ten cases (42 per cent). Sudden death occurred in all but four cases, and in most of them it occurred presumably from rupture of the aneurysm. The high

incidence of positive Wassermann reactions of the blood occurred in this group, namely, 83 per cent. Examinations of the spinal fluid were conducted in all cases, and 25 per cent showed positive reactions. Associated syphilitic manifestations were revealed in five cases. As anticipated, the incidence of electrocardiographic abnormalities was small; only four instances (17 per cent) occurred. In four cases, significant T-wave negativity was disclosed, and delayed auriculo-ventricular conduction was found in one case.

DISCUSSION

Although the number of cases comprising this study is relatively small, the data derived from them are probably fairly reliable and representative of the course of cardiovascular syphilis.

The relatively long periods of apparent latency that occur in syphilis have been emphasized by many writers on the subject. In keeping with the observation, a relatively long average period of time elapses from the initial syphilitic infection until death occurs from cardiovascular involvement. Even though this period is relatively long, death occurs considerably earlier in life than the age at which death would be anticipated in normal persons.

It was not possible to draw any definite conclusions concerning the influence of treatment on the course of the disease. Much of this information could be derived only by inquiry, and in many of the cases it was so inaccurate and uncertain as to be of no value.

TABLE I
SUMMARY OF DATA

| | CASES | AVERAGE AGE OF OCCURRENCE OF SYPHILIS, YEARS | AVERAGE AGE AT TIME OF DEATH FROM CARDIO- VASCULAR DIS- EASE, YEARS | AVERAGE DURA- TION OF COURSE, YEARS |
|---|-------|--|---|---|
| Group I, syphilitic aortitis | 17 | 31 | 54 | 23 |
| Group II, syphilitic aortitis with aortic insufficiency | 59 | 26 | 49 | 23 |
| Group III, thoracic aneurysm | 24 | 27 | 53 | 26 |

THE DIAGNOSIS OF SYPHILITIC AORTITIS WITH NEGATIVE WASSERMANN REACTIONS*

SAMUEL A. LEVINE, M.D.

BOSTON, MASS.

THE clinical diagnosis of syphilitic aortitis is often difficult and sometimes impossible. This is particularly true under certain circumstances. There are three conditions which enable us either to suspect the diagnosis or at least to avoid overlooking it. These are the presence of a definite aneurysm of the aorta, made out either by physical or x-ray examination, the finding of aortic insufficiency or the presence of a positive Wassermann reaction in the blood. The occurrence of any one of these three findings should be sufficient to focus our attention on syphilis as the possible underlying factor in any cardiovascular case. The purpose of this brief review is to find how frequently the above criteria are absent in proved cases of syphilitic aortitis and to see whether there are any means available for recognizing the condition at the bedside. An analysis was, therefore, made of all the cases of syphilitic aortitis that came to autopsy at the Peter Bent Brigham Hospital. There were forty such cases available for this study.

Of the 40 proved cases of lnetic aortitis 12, or 30 per cent, had negative Wassermann reactions in the blood. The number of blood tests varied from one to three and in no case was a provocative test done. All the Wassermann reactions were carried out under the same standard conditions. A few cases were considered as positive although the test at the hospital was negative, because it was known that at some previous time the test had been positive. It is clear that we must be ready to diagnose syphilitic aortitis even in the face of a negative Wassermann, for in 30 per cent of the cases the test failed to give the desired information. It is believed by some, and there is evidence to support the view, that this percentage would be further diminished if provocative tests were carried out.

As has been mentioned above, the finding of an aortic diastolic murmur indicating aortic regurgitation should direct our attention to syphilitic heart disease. This is especially true when it is found in individuals around the age of forty or over. The two other conditions in which aortic regurgitation frequently occurs are rheumatism and arteriosclerotic hypertensive heart disease. In general, it may be said that aortic insufficiency occurring in individuals under forty years of

*From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.
Read by title.

age in the absence of obvious well-marked hypertension, is apt to be rheumatic in origin. There were three cases, however, thirty-eight and thirty-nine years old, in this series in which syphilitic aortitis without aortic insufficiency was present. If the series were larger, no doubt instances would have been found of comparatively young patients with luetic aortic insufficiency. The problem of distinguishing rheumatic from syphilitic aortic insufficiency becomes increasingly difficult at times because of the frequency of the negative past history of syphilis in the syphilitic cases and of a negative rheumatic history in the rheumatic cases. In this connection it is helpful to uncover evidence of stenosis of either the mitral or the aortic valves, for when such findings are made out, one may be quite certain that the condition is rheumatic and not syphilitic. There was no instance of stenosis of the mitral or aortic valves in these 40 cases and although such a case might be found, it must be a rare occurrence. There were 17 cases showing definite aortic regurgitation. This means that in somewhat more than half of our patients the syphilitic process in the aorta did not extend to the valves, which remained competent. The inference, however, may well be made that any patient forty years old or over who has aortic insufficiency and no stenosis of any of the valves should be regarded as possibly syphilitic.

The discovery of a definite aneurysm of the aorta as distinguished from a slight dilatation of the aorta so frequent in hypertension should be considered as a positive evidence of syphilis. At times the distinction between a true aneurysmal formation and a diffuse dilatation of the aorta is not simple. Careful x-ray examination is extremely valuable in making this differentiation. There were 17 cases showing evidence of aneurysm at autopsy. In only 12 of these cases was the diagnosis of aneurysm made clinically. In 7 of these 17 there was aortic regurgitation and that was sufficient to direct our attention to a syphilitic process.

A careful review of the clinical data of these cases showed that in some the diagnosis was quite evident from the findings on physical examination. In others, the history of pain in the upper chest or suffocation and cough was sufficient to direct our attention to aneurysm of the aorta as the cause of the complaint. There remained a few, however, in whom the aneurysm produced no physical signs that were detectable and no particularly characteristic symptoms. Here the x-ray examination was practically the only means of detecting the underlying condition. A more liberal use of x-ray and fluoroscopy of the aorta and a more careful roentgenological interpretation of these findings would certainly enable us to detect some cases of aneurysm of the aorta that would otherwise be overlooked.

The past history of syphilitic infection was of uncertain value in this group of patients. In only 18 was there either a definite history

of syphilis or sufficient related features to make one suspect that the patient was luetic. In this connection the finding of Argyll-Robertson pupils or characteristic changes in the spinal fluid is most important. It follows from this that in a little less than one-half of the cases, the history itself might direct our attention at a proper diagnosis, but that in the other half no such aid in the history would be obtainable. It is very questionable how much real help one obtains from the presence or absence of a past history of repeated miscarriages. There are so many nonsyphilitics who have had repeated miscarriages and so many syphilitics who have not.

It is interesting to analyze more intimately the 12 cases that had a negative blood Wassermann reaction. Of these there were 4 that had definite aortic insufficiency, two of which in addition had an aneurysm of the aorta, and a positive past history of syphilis. Of the other two the past history was positive in one and negative in the other. There were also 4 of these 12 who had an aneurysm of the aorta and no aortic insufficiency. Of these 4 the past history was positive in one, negative in two, and questionable in the other. There remain 4 cases of definite luetic aortitis in this series that showed no evidence of aneurysm or aortic insufficiency and had a negative past history of lues and showed a negative Wassermann reaction in the blood. This would indicate that in 10 per cent of our cases all of the above distinctive features that might direct one's attention to a luetic process were absent. (Cases 9, 30, 31, and 37.) If cases of the type of the last four are to be recognized clinically, the diagnosis will have to be made on indefinite evidence of a character that may be regarded as suspicious, or more careful interpretation of the x-ray findings in the aorta and possibly on a more liberal use of a provocative Wassermann test.

HISTORY OF CASES WITH NEGATIVE WASSERMANN

CASE 4.—A fifty-six-year-old white man died having shown signs of definite aortic regurgitation and aortic aneurysm. The aneurysm was discovered by x-ray examination. He gave a history of primary infection but the Wassermann was negative on two occasions.

CASE 9.—A forty-five-year-old white woman died of bronchial pneumonia three days after entering the hospital. There was no past history of lues and the heart examination was negative. Autopsy showed bronchial pneumonia and luetic aortitis.

CASE 11.—A fifty-three-year-old white man died having shown definite evidence of aortic insufficiency and aneurysm. There was a positive past history of lues. The Wassermann test was negative on two occasions. The autopsy showed a rupture of an aortic aneurysm into the right pulmonary artery.

CASE 15.—A sixty-one-year-old white man entered the hospital complaining of pain and swelling in the right upper quadrant, cough, and dyspnea. There was a questionable old history of lues. Examination showed an enlarged heart, a to-and-fro pericardial friction, a markedly enlarged liver, and signs of pneumonia of the right lower lobe. Autopsy showed a definite aortic aneurysm and luetic aortitis.

CASE 18.—A sixty-three-year-old Spaniard entered the hospital in delirium. There was a past history of lues. Examination of the heart was negative. There was evidence of tumor of the brain for which he was operated on and died a few days later. Autopsy showed carcinoma of the lung, metastasis to the brain, luetic aortitis, and a small aneurysm of the aorta.

CASE 20.—A thirty-year-old colored woman entered the hospital complaining of cough, weakness, nausea, vomiting, and increasing dyspnea. There was no past history of lues, although she had had two miscarriages. The heart was enlarged and there was a systolic murmur over the precordium. Wassermann was negative on two occasions. The clinical diagnosis was luetic aortitis which was confirmed by post-mortem examination.

CASE 28.—A seventy-three-year-old sailor entered the hospital complaining of dyspnea and scaling eruption of the lower legs. There was a history of lues at the age of twenty-three. Examination showed marked evidence of aortic insufficiency. Autopsy showed luetic aortitis.

CASE 30.—A forty-nine-year-old white woman entered the hospital complaining of dyspnea. Past history was negative except for two miscarriages. Seventeen years previously there were ulcers of both eyes. No history of lues. One year ago she had fainting and dizzy spells with increasing dyspnea. Examination showed a moderately enlarged heart with no murmurs. There was evidence of old glandular tuberculosis of the neck and some involvement of the apices of the lungs. X-ray examination showed dilatation of the aorta. Wassermann was negative. Autopsy revealed chronic nephritis and luetic aortitis. In this case the x-ray findings and the other secondary features of the case should be sufficient to make one strongly suspect syphilis, even in the absence of a positive Wassermann reaction.

CASE 31.—A sixty-year-old white man entered the hospital with lobar pneumonia, from which he died in a few days. Examination of the heart was entirely negative. There was no history of lues and no previous symptoms indicating circulatory disease. Autopsy showed lobar pneumonia and luetic aortitis. In this case the syphilitic process was silent and there was no way of suspecting it during life.

CASE 35.—A thirty-year-old Italian entered the hospital complaining of weakness and dyspnea. There was a definite past history of rheumatic fever but not of syphilis. Wassermann test was negative. Examination showed an enlarged heart with signs of aortic insufficiency. During life he was considered as having rheumatic heart disease. At autopsy it was found that he had luetic aortitis. This presents an extremely difficult problem in differential diagnosis. The only way such errors might be avoided is if, on careful x-ray examination of the aorta, additional data could be obtained. In rheumatism the aorta remains essentially unchanged whereas in syphilis irregularities of contour or localized dilatations occur.

CASE 36.—A sixty-four-year-old woman entered the hospital complaining of shortness of breath and substernal pain. There had been two miscarriages and two children died in infancy. Examination showed irregular pupils and enlarged heart and increased suprasternal dullness. The left radial pulse was much greater than the right. Distinct pulsation could be seen in the second left interspace. Autopsy showed a syphilitic aneurysm of the ascending aorta with extension into the right ventricular wall. Here, despite the negative Wassermann, there were sufficient data to make a clinical diagnosis of syphilis of the aorta.

CASE 37.—A forty-six-year-old white man entered the hospital complaining of dyspnea, palpitation, and pain in the abdomen. There was no history of lues and nothing pointing to aortic disease on examination. Clinically, the diagnosis was

hypertension, hyperthyroidism, and acute cholecystitis. Pathological examination showed well-marked luetic aortitis. In this case, as in Case 31, it would be difficult to make a proper diagnosis in the absence of a positive Wassermann, as there was very little to make one suspect syphilis either in the history or on the examination.

SUMMARY

In this review of 40 cases of syphilitic aortitis as determined by post-mortem examination, the Wassermann reaction in the blood was negative in 12 instances. An attempt was made to analyze the means we have apart from the Wassermann test that would enable us either to diagnose the condition during life, or at least to avoid overlooking its possibility. When there is evidence of aortic insufficiency or definite evidence of aneurysm of the aorta, that should be sufficient to direct our attention at lues as a possible cause. The same may be said of a positive past history of syphilis and of evidence of syphilis of the central nervous system. There remained, however, 4 cases in which there was no history of syphilis and no evidence of either aneurysm or aortic insufficiency. Such cases might be diagnosed in life by more careful roentgenological study, by an occasional finding of a positive Wassermann only after a provocative test, combined with other clinical data that in general point to syphilis.

THE RELATION OF SYPHILIS TO HYPERTENSION (STATISTICAL STUDY)*

EMMET F. HORINE, M.D., AND MORRIS M. WEISS, M.D.

LOUISVILLE, KY.

PATIENTS are encountered who have syphilis and hypertension. What relationship, if any, exists between the two conditions? Do syphilitic patients exhibit hypertension to a greater degree than non-syphilitic patients? Is the incidence of syphilis greater among hypertensive individuals than among a group of controls? These are some of the questions that thus arise, and a cursory search of the literature reveals confusing statements concerning the etiological relationship.

The etiological importance of syphilis is stressed by Faught¹ who states that "syphilis is well recognized as a cause of hypertension." Stoll,² finding that of fifty cases of hypertension, 90 per cent gave either a positive Wassermann or luetin test or were known to have lues or to have children with hereditary syphilis, claims that hypertensive disease is the most common of the so-called "late" manifestations of hereditary syphilis. Brin and Giroux³ are of the opinion that syphilis is one of the principal causes of arterial hypertension. Smith⁴ asserts that syphilis is often associated with high blood pressure and that hypertension is also a frequent corroborative sign in such cardiovascular conditions as aneurysm and syphilitic aortitis. Mattei and Toinon⁵ studied 210 hypertensives and found syphilis the only etiological factor in thirty cases.

Contrasted with the opinions just mentioned Pellissier⁶ believes that there is no such clinical entity as syphilitic hypertension. Davison and Thoroughman⁷ in a study of heart disease in the negro race state that in their series of cases with combined syphilis and hypertension syphilis *per se* had nothing to do with the causation of hypertension any more than another toxic or infectious condition might. Keith, Wagener and Kernohan,⁸ finding a positive Wassermann only once in seventy-five cases of malignant hypertension, believe that syphilis is not etilogically important in this condition. Steinfield, Pfahler and Klauder⁹ state that syphilis apparently plays no part in hyperpiesia, especially of the climacteric group. Fishberg¹⁰ does not believe that syphilis is a causative factor in essential hypertension.

The incidence of syphilis in hypertension has been variously reported. For example McElroy¹¹ noted a positive Wassermann in only 5 of 100 cases of essential hypertension while Stone and VanZant¹² found that of 436 patients with hypertensive heart disease 28.3 per

*From the Medical Department, University of Louisville, School of Medicine.

cent had syphilis. McLester¹³ found a positive Wassermann in 17.5 per cent of 124 patients with hypertension. R. F. Weiss¹⁴ analyzed 56 cases of essential hypertension from an etiological point of view and found syphilis in 8.9 per cent of the cases. Palmer¹⁵ found no instance of syphilis in 81 young male adults with a systolic blood pressure of 150 mm. Hg. or over. Vaquez¹⁶ found syphilis to be present in 78 of 100 hypertensive individuals and Amblard¹⁷ found syphilis in 78 per cent of his hypertensive patients. In a study of the cardiovascular findings in women with syphilis, Arnett¹⁸ found that 8.3 per cent of the cases of tertiary syphilis had arterial hypertension as against 5.1 per cent of the control group.

Because of such conflicting statements as cited above, a study was undertaken of 666 cases of essential hypertension admitted to the wards of the Louisville City Hospital from 1925 to 1930. Two thousand control admissions were likewise studied. A positive Wassermann was considered evidence of a syphilitic infection; although we are well aware that syphilis may be present in an individual with a negative Wassermann. No attention was paid to the history alone of a primary sore or secondary eruption. Statements of our city hospital patients and especially negroes are notoriously unreliable in respect to such lesions. We included in our study only those cases which were sufficiently complete as to lend themselves to statistical analysis. No known cases of secondary hypertension were included. An especial attempt was made to exclude cases of chronic diffuse nephritis with coexisting hypertension from cases of essential hypertension with varying degrees of renal insufficiency. Where a differentiation could not be made in a given case, it was not included in the study. Although some nephritic hypertensive patients may have been included, they are probably too few in number seriously to affect the final conclusions.

A systolic pressure of 150 mm. Hg. or a diastolic pressure of 100 mm. Hg. constantly maintained was arbitrarily considered the lower limits for hypertension. No attempt was made to calculate the expected average blood pressure from the height, weight and age, since all the cases had a blood pressure well within the hypertensive level. An exception to this is a carefully selected group of 68 cases with normal or low blood pressure and cardiac enlargement but without any valvular lesion present or other factor that might produce the cardiac enlargement. We believe that such patients must of necessity fall in the hypertensive group even though the previous level of the blood pressure is unknown. Ophthalmoscopic signs of a preexisting hypertension frequently will be found. Roentgenologic examination may furnish suggestive proof of the presence of a previous hypertension because of the cardiac silhouette. In addition, impairment of renal function or even uremia may be present. Electrocardiographically marked left axis deviation and frequently the coronary types of elec-

trocardiograms are encountered here, such as are so often found in the known hypertensive individuals. While this type of electrocardiogram does not of itself evidence preexisting hypertension, its presence with an unexplained cardiac enlargement, eye-ground signs and findings of renal impairment, is suggestive evidence of the previous elevated state of the blood pressure. In hypertensive cases the development of a coronary occlusion results in a marked lowering of the blood pressure to normal or even subnormal levels. Furthermore, in twenty years of recorded blood-pressure observations we have had personal opportunity to watch certain patients who first merely presented hypertension, later gradually developed cardiac hypertrophy, still later presented electrocardiographic evidence of coronary changes and who, following an acute coronary occlusion or the onset of congestive heart failure, finally showed a marked lowering of the blood pressure. The arteriolarsclerotic or primary contracted kidney which always evidences a hypertension during the life of the individual will be found at autopsy in these cases. We have elsewhere reported (December 2, 1929) a selected group of such cases.¹⁰

Of the 666 patients studied, 526, or 79 per cent, had a negative Wassermann while 140, or 21 per cent, had a positive serum reaction. The group investigated included 369 negroes and 297 whites. Of the 369 negroes 112, or 30.4 per cent, had positive Wassermans whereas only 9.4 per cent of the whites had serological evidence of the infection (Table I). The relatively high percentage of syphilis as found in the combined group is thus the result of the marked incidence of syphilis among the negro hypertensive patients.

Of a control group of 2000 Wassermann tests on patients aged thirty to ninety years in the various clinics and wards of the Louisville City Hospital, 25.5 per cent had a positive Wassermann. This compares fairly closely with the percentage incidence of syphilis in the hypertensive group. Of the negroes numbering 967 in the control group, 316 or 32.6 per cent had a positive Wassermann (Table II).

TABLE I
HYPERTENSIVES ANALYZED ACCORDING TO WASSERMANN REACTION AND RACE

| WASS. | TOTAL | PER CENT | WHITE | PER CENT | NEGRO | PER CENT |
|-------|-------|----------|-------|----------|-------|----------|
| - | 526 | 79 | 269 | 90.5 | 257 | 69.6 |
| + | 140 | 21 | 28 | 9.5 | 112 | 30.4 |
| | 666 | | 297 | | 369 | |

TABLE II
CONTROL GROUP ANALYZED ACCORDING TO WASSERMANN REACTION AND RACE

| WASS. | TOTAL | PER CENT | WHITE | PER CENT | NEGRO | PER CENT |
|-------|-------|----------|-------|----------|-------|----------|
| - | 1489 | 74.5 | 838 | 81.2 | 651 | 67.4 |
| + | 511 | 25.5 | 195 | 18.8 | 316 | 32.6 |
| | 2000 | | 1033 | | 967 | |

The difference in the incidence of syphilis in hypertensive individuals as noted by various observers thus largely depends upon the prevalence of syphilitic infection in the particular class of patients studied. McLester¹³ found syphilis in 17.5 per cent of his hypertensives, because 16.5 per cent of his patients in general had a positive Wassermann. Palmer,¹⁵ studying young college men, found no instance of syphilis in those with hypertension and his control group was similar, showing a syphilitic rate of only 0.8 per cent. Pellissier⁶ encountered syphilis in 26 per cent of 60 cases of essential hypertension in contrast to an incidence of 20 to 22 per cent in the population as a whole.

Table III shows the distribution of cases of our hypertensive group according to sex. There was practically no difference in the incidence of syphilis in the sexes of both colors. Of the 392 males, 87 or 22.2 per cent, had a positive Wassermann as against 53 females, or 19.4 per cent. The white males had a syphilitic rate of 8.1 per cent in contrast with the negro male rate of 35.2 per cent and the female whites had a positive rate of 11.8 per cent against the female colored group with a rate of 24.4 per cent. In the control group the distribution of syphilis among the sexes of both the white and negro patients is practically the same as in the hypertensive group (Table IV).

TABLE III

HYPERTENSIVES ANALYZED ACCORDING TO WASSERMANN REACTION, RACE AND SEX

| <i>Males</i> | | | | | | |
|----------------|-------|----------|-------|----------|-------|----------|
| WASS. | TOTAL | PER CENT | WHITE | PER CENT | NEGRO | PER CENT |
| - | 305 | 77.8 | 172 | 91.9 | 133 | 64.8 |
| + | 87 | 22.2 | 15 | 8.1 | 72 | 35.2 |
| | 392 | | 187 | | 205 | |
| <i>Females</i> | | | | | | |
| - | 221 | 80.6 | 97 | 88.2 | 124 | 75.6 |
| + | 53 | 19.4 | 13 | 11.8 | 40 | 24.4 |
| | 274 | | 110 | | 164 | |

TABLE IV

CONTROL GROUP ANALYZED ACCORDING TO WASSERMANN REACTION, RACE AND SEX

| <i>Males</i> | | | | | | |
|----------------|-------|----------|-------|----------|-------|----------|
| WASS. | TOTAL | PER CENT | WHITE | PER CENT | NEGRO | PER CENT |
| - | 756 | 70.7 | 466 | 79.7 | 290 | 59.8 |
| + | 313 | 29.3 | 118 | 20.3 | 195 | 40.2 |
| | 1069 | | 584 | | 485 | |
| <i>Females</i> | | | | | | |
| - | 733 | 78.8 | 372 | 82.9 | 361 | 74.9 |
| + | 198 | 21.2 | 77 | 17.1 | 121 | 25.1 |
| | 931 | | 449 | | 482 | |

The distribution of the cases according to age is shown in Table V. The largest number of cases, 90 per cent, occurred in the fifth to the ninth decades inclusive, as occurs in hypertension in general. The

highest incidence of patients with positive Wassermanns occurred in the fourth, fifth and sixth decades as might be expected.

A thorough study of combined syphilitic and hypertensive heart disease was not attempted. We are in accordance with Arnett, who believes that since the physical signs of syphilitic aortitis without aortic regurgitation are frequently found in patients with hypertension, it is impossible in most cases of syphilis with hypertension to determine clinically whether or not syphilitic aortitis is present. Fourteen cases with a positive Wassermann had frank aortic insufficiency without a high pulse pressure. Two of these patients had roentgenological signs of an aortic aneurysm, and the only case which came to autopsy showed a large aneurysm of the arch of the aorta with an extension of the process to the aortic valve producing an aortic insufficiency. We are unable clinically to determine in these cases of aortic insufficiency whether the hypertension or the syphilis or both were responsible for the valvular lesion. It is well known that syphilitic aortitis and hypertension may coexist. In a study of heart disease in the negro race, Davison and Thoroughman⁷ found that of 65 patients with syphilitic heart disease, 16 had a coincident hypertension. Stone and Vanzant¹² in a survey of heart disease in a southern clinic state that at autopsy pathologists often demonstrated greatly enlarged hearts without valve defects so characteristic of hypertensive heart disease but with a coincident typical syphilitic aortitis. Smith⁴ claims that hypertension is a frequent corroborative sign in such cardiovascular conditions as aneurysm and often in syphilitic aortitis. Fishberg¹⁰ confirms Gallavardin's²⁰ observation that the combination of syphilitic aortitis and hypertension is uncommon.

The problem of the etiology of hypertension still remains an enigma. Janeway²¹ has well said that the "range of possible etiological factors as found in the life history of patients was so great as to demand an extensive critical study to yield anything more than the usual textbook catalogue of all the diseases and vices of the human race." The French authorities have, in general, stressed the possibility that syphilis has an important bearing on hypertension. They probably felt that since syphilis attacks the heart and vascular system hypertension might be the expression of such invasion. Our present concept of essential hypertension as an arteriolar disease would seem to preclude any such possibility. Further, the microscopical findings in syphilitic involvement of the arteries are radically different from those in hypertension. Another reason why syphilis has been suspected as a cause for hypertension is the fact that in certain groups studied syphilis was the only condition found in the past history of the patient. However, we have shown that in carefully controlled groups syphilis has been an equally striking factor.

SUMMARY

A group of 666 patients with essential hypertension was studied to determine if syphilis were a possible etiological factor. A control group of 2000 nonhypertensive patients of similar ages and economic status was studied. The incidence of syphilis was practically the same in the hypertensive group as in the control group. Syphilis cannot have any etiological bearing on essential hypertension.

REFERENCES

1. Faught, F. A.: Blood Pressure, Philadelphia, 1916, page 252, W. B. Saunders Co.
2. Stoll, H. F.: The Rôle of Syphilis in Hypertensive Cardio Vascular Disease, *Am. J. M. Sc.*, 150: 178, 1915.
3. Brin, L., and Gironx, L.: Syphilis du Cœur et de l'Aorte, Paris, 1924, page 51, Gaston Doin.
4. Smith, S. Calvin: Heart Affections—Their Recognition and Treatment, Philadelphia, 1920, page 131, F. A. Davis Co.
5. Mattei, C., and Toinon, C.: Effect of Specific Treatment on Hypertension in Syphilitics, *Bull. gén. de thérap.*, 178: 289, 1927.
6. Pellissier, L.: L'Hypertension Artérielle Solitaire, Paris, 1927, page 75, Masson & Cie.
7. Davison, H. M., and Thoroughman, J. C.: A Study of Heart Disease in the Negro Race, *South. M. J.*, 21: 464, 1928.
8. Keith, N. M., Wagner, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, *Arch. Int. Med.*, 41: 141, 1928.
9. Steinfeld, E., Pfahler, G. E., and Klander, J. V.: Clinical and Roentgenological Study of One Hundred and Five Cases of Syphilis with Reference to the Cardio-vascular System, *Arch. Int. Med.*, 32: 556, 1923.
10. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, 1930, page 456, Lea & Febiger.
11. McElroy, J. B.: Benign Hypertension, *Tice's Practice of Medicine*, 6: 660, 1922.
12. Stone, C. T., and Vanzant, Frances R.: Heart Disease as Seen in a Southern Clinic, *J. A. M. A.*, 89: 1473, 1927.
13. McLester, J. S.: The Causes of Arterial Hypertension, with Special Reference to Syphilis—A Clinical Inquiry, *Am. J. Syph.*, 1: 746, 1917.
14. Weiss, R. F.: Ueber Konstitutionelle familiäre Hypertonie, *Med. Klin.*, 21: 1049, 1925.
15. Palmer, R. S.: The Significance of Essential Hypertension in Young Male Adults, *J. A. M. A.*, 94: 694, 1930.
16. Vaquez, H.: Appareil Circulatoire, Paris, 1923, page 781, Masson & Cie.
17. Amblard, L. A.: L'hypertension artérielle permanente suivant l'âge, pathogenie et valeur semeiologique, *Paris Med.*, 11: 48, 1913.
18. Arnett, John H.: Cardiovascular Findings in Women with Syphilis, *Am. J. M. Sc.*, 176: 65, 1928.
19. Horine, Emmet F., and Weiss, Morris M.: Hypertensive Heart Disease Without Hypertension, *Kentucky Med. Jour.*, 28: 464, 1930.
20. Gallavardin, L.: La Tension artérielle en Clinique, Paris, 1920, page 369, Masson & Cie.
21. Janeway, Theodore C.: A Clinical Study of Hypertensive Cardiovascular Disease, *Arch. Int. Med.*, 12: 755, 1913.

CLINICAL HEART FINDINGS IN CHILDREN WITH CONGENITAL SYPHILIS

GIUSEPPE PREVITALI, M.D., GERTRUDE H. B. NICOLSON, M.D., AND
D. MOON-ADAMS, M.D.

NEW YORK, N. Y.

REPORTS on the clinical heart findings in congenital syphilis are meager in comparison to the extended studies made on other phases of the disease. Pathological examinations, dating from Rosen's description in 1860 of gummata in the heart of a newborn infant, are fairly numerous and give a definite picture of changes in the myocardium and great vessels occasionally found at autopsies of congenital luetics. However, it is noteworthy that the great majority of such reports deal with fetuses or with infants of less than one year. The impetus given to the study of heart disease in acquired syphilis, when Heller in 1899 pointed out its relationship to aortitis, apparently did not extend to congenital syphilis. Moreover, there is divergence of opinion among those who have studied the subject as to frequency and manifestation of heart involvement.

Alfred Friedlander in a paper read before the thirty-third meeting of the American Pediatric Society in 1921, maintained that myocardial degeneration in children was frequently caused by syphilis and falsely attributed to other infections.

Stolkind¹ in 1920, after reviewing the literature, concluded that no proved case of aortitis in congenital syphilis had been reported and surmised that congenital syphilitics with heart involvement did not survive birth long enough to give clinical manifestations.

Warthin² reported a case of acute syphilitic myocarditis in a man of twenty-five years suffering from congenital syphilis. He also reported autopsies on two infants who showed spirochetes in the heart muscle with absence of any other luetic lesions, and suggested that this may be a more frequent cause of sudden death than is commonly recognized.

Matusoff and White³ published a pathological study of 35 cases of congenital syphilis autopsied at the Massachusetts General Hospital and the Infants and Child Hospital in Boston, and a clinical study of 25 cases under treatment. Fourteen, or 40 per cent, of the first group showed luetic changes in the heart or blood vessels. In the second group studied for clinical signs they found no cardiac involvement attributable to lues.

In view of such conflicting reports, we thought it of interest to examine the heart in fifty cases of congenital syphilis, under active treat-

ment at Bellevue. Our plan of procedure was first to verify the diagnosis of congenital syphilis by physical signs and by a family history and blood tests on the parents and siblings. The past history of each case was thoroughly investigated to eliminate the possible complication of rheumatic infection, and no child in this group had had endocarditis, acute rheumatic fever, joint pains, frequent sore throats or chorea. Only four gave histories of occasional sore throats. In one an effusion without fever or redness was present in both knee joints which cleared up under antiluetic treatment and was diagnosed luetic arthritis.

Complete physical examination was made recording the general constitution and habitus of the child. Teleroentgenograms and electrocardiograms were taken on each patient. Record was made of treatment received prior to examination, the age at which treatment was started, the blood Wassermann report on admission and also at the time of examination. Finally the cases were grouped by their age and sex.

Our study included 28 girls and 22 boys; the youngest was four weeks of age and the oldest fourteen years. Forty-six of the 50 were under eleven years, 14 under two years and 9 under one year. In every case the blood Wassermann was 4 plus on admission. At the time of examination 32 cases had 4 plus Wassermann reports, 3 had 1 plus, 1 had 2 plus and 14 had negative Wassermans.

The latter group comprised children who had been under treatment for varying periods extending from three months to twelve years. Seven children were examined before receiving treatment.

The group showed no symptoms of tachycardia or dyspnea on exertion, or other signs suggesting a cardiac syndrome. On physical examination of the heart no abnormal pulsation, precordial bulging, marked venous tracing or cyanosis was noted. No instance of clubbing of fingers or toes was seen. The point of maximum cardiac impulse was found in each case to be within normal limits, and the percussed borders showed no enlargement. On auscultation no murmurs of organic type were heard. In eight cases systolic murmurs were heard at the base or apex which, because of their location, their lack of transmission and variable intensity were classified as functional. To record blood pressure a sphygmomanometer with child cuff was used and readings were taken from the arm, or in small infants from the leg. Eleven readings have been omitted from this study, judged inaccurate, in one instance because the patient had an evident glandular dyscrasia as a basis for his hypotension, and in the others because a uniform reading seemed impossible on account of the constant crying of these infants. In the remaining 39 cases the average pressure was

93 mm. systolic with a diastolic of 51 mm., giving an average pulse pressure of 42 mm. This is somewhat higher than that found in normal children. Our highest systolic blood pressure was 125 in a boy of nine years and the lowest 82 in a girl of two years. The diastolic pressure was audible to zero in three children, but as a change in the intensity of the pulsation was heard at a some higher level, this degree was taken as the diastolic reading.

The roentgenograms were taken at a distance of six feet except in nine infants on whom flat plates were made. The sthenic type of heart predominated, being present in 28 cases. Hypersthenic hearts were seen in 6 cases and hyposthenic in one. Among the 9 infants on whom flat plates were taken no apparent enlargement was seen. The 35 teleroentgenograms showed no increase in the ratio between the transverse diameter of the heart and that of the pulmonic field except in two instances where the hearts were of the hypersthenic type.

In twelve cases the right auricular curve and in one both auriculars were accentuated. In one instance the left auricular and the left ventricular curve, and in another the ventricular alone was accentuated. Two children with negative clinical findings showed an accentuation of the curve of the pulmonic artery. No case showed widening of the aortic arch.

Electrocardiograms were obtained on all of the 50 children. Their rhythm was of the regular sinus type in all instances. In one case, a crying infant, this was interrupted by occasional premature auricular contractions. Sinus arrhythmia was frequently present, simple tachycardia was noted nine times, and bradycardia once. Low voltage was noted in 14 records. Conduction between auricles and ventricles was in no case delayed; there was no defect found in the bundle or its branches. Axis deviation was equally distributed, being present five times to the right and five to the left. The individual deflections did not differ from the normal. P_3 was not found inverted and T_1 and T_2 were always upright. The R-wave in Lead I was commonly of poor amplitude.

SUMMARY OF FINDINGS IN FIFTY CASES OF CONGENITAL SYPHILIS

1. Physical examination of the heart was negative.
2. Rheumatic lesions were not present.
3. Average blood pressure was 93/51, giving a pulse pressure of 42, the normal being from 27 to 30.
4. Thirty-five teleroentgenograms showed normal ratio between transverse cardiac diameter and pulmonic fields. The aortic arch was in no case widened.
5. Electrocardiograms showed normal rhythm with no delay in conduction, no abnormalities of deflection, but frequent low voltage.

6. The findings in children who had received no treatment were the same as in those whose Wassermanns had been rendered negative by treatment.

7. Children of varying age groups showed no differentiation in their physical signs.

CONCLUSION

In contrast to the findings in acquired syphilis, we were not able to detect, by available methods of physical examination, any cardiovascular lesion in the fifty cases of congenital syphilis examined.

REFERENCES

1. Stolkind, E. S.: *Brit. J. Child. Dis.*, 17: 126, 1920.
2. Warthin, A. S.: *Am. J. Syph.*, 10: 1, 1926.
3. Matusoff, Irving, and White, Paul D.: *Am. J. Dis. Child.*, 34: 390, 1927.

HEART DISEASE IN CHILDREN DUE TO CONGENITAL SYPHILIS*

THURMAN B. GIVAN, M.D.

BROOKLYN, N. Y.

MY CONTRIBUTION to this symposium consists in the analysis of more than four hundred cases of congenital syphilis. These were selected from cases with outstanding symptoms of the disease, such as young infants with florid skin and visceral lesions, the older child with interstitial keratitis, joint signs, or central nervous symptoms. The total number of cases of this disease observed during the past ten years exceed two thousand. In collecting this data, autopsy records, x-ray reports, electrocardiographic reports, laboratory findings, etc., were used from the Long Island College and Brooklyn Eye and Ear Hospitals. Most of the cases have been observed for several years, and a majority have had a cardiac examination during the past two years. Until two years ago very little attention was directed to the heart in these cases; however, clinical examinations were done on practically all cases, as well as on those in this series. When the *Spirochaetae pallidae* invade the blood stream of the unborn infant, obviously, a septicemia begins, and, depending upon several factors, for example, the virulence and the selectivity of the invader, vital organs and tissues of the body are injured. This injury seems to vary in degree; hence anything from a macerated fetus to a perfectly well-developed, living infant may be delivered. Autopsy records in the former show the *Spirochaetae pallidae* in the various tissues of the body, notably the liver, the spleen, the lungs, the osteochondral portions of the long bones, and many times in the heart, particularly the myocardium. These infants, if not born dead, usually die during the first three or four months after birth, with or without treatment.

In no case has the autopsy protocol shown sufficient changes in the heart to account for death, although interstitial myocarditis and vacuolization of the muscle fibers have been demonstrated. Usually a terminal pneumonia and now and then a syphilitic meningitis account for death. Except to the pediatricist and the syphilologist these cases are only of academic interest. The question you are interested in is, what happens to the heart and aorta of the child with congenital syphilis as he grows up? Undoubtedly some of these infants with spirochetal invasion of the heart and other visceral organs, if treated early, survive and actually do grow up.

*From the Department of Pediatrics, Long Island College Hospital, Brooklyn, and the Congenital Syphilis Clinic of the Brooklyn Eye and Ear Hospital, Brooklyn.

Table I shows 404 cases of congenital syphilis divided into age groups. One hundred and seventeen had a physical examination with especial reference to their hearts before receiving any antisyphilitic treatment. Many had x-ray, fluoroscopic, electrocardiographic, blood pressure and clinical examinations. In no case was anything referable to cardiac damage found. Likewise 287 patients who had received antisyphilitic treatment had similar examinations; in none of these did the heart show any abnormalities. The fact that the pulmonic second in children presents normally a louder sound than the aortic second was an aid in reaching the above conclusion. Any case showing A_2 equal to or louder than P_2 was selected for a more careful survey. The older the age group, naturally, the more were there of these cases.

TABLE I
NO SIGNS OF HEART DISEASE

| AGE | UNTREATED CASES | TREATED CASES | CASES WITH INTER- STITIAL KERATITIS |
|-------------------------|--------------------|------------------|--|
| Under one year | 8 | 5 | 0 |
| Between 1 and 2 years | 4 | 3 | 0 |
| Between 2 and 5 years | 17 | 15 | 13 |
| Between 5 and 10 years | 44 | 78 | 51 |
| Between 10 and 16 years | 36 | 133 | 96 |
| Between 16 and 30 years | 5 | 48 | 45 |
| Over 30 years | 3 | 5 | 7 |
| Total | 117 | 287 | 212 |

Those showing interstitial keratitis are included in the tabulation for the reason that these cases occur usually only as a lighting-up process in congenital syphilis tarda. During this period of activation one might expect cardiac changes, but in our experience such is not the case.

Taking for granted that syphilitic heart changes take place on an average of eighteen to twenty years after the primary infection in acquired syphilis, a special effort was made to follow up those cases of congenital syphilis more than sixteen years of age. Sixty-one of such showed no cardiac abnormalities.

It might be said of the 287 treated cases that some of these might have developed heart changes had they not been treated. This obviously cannot be answered. Many of them, however, had been examined previously, a large number during infancy, with no notation of cardiac disease.

Syphilologists who have had large experiences in treating organic heart conditions due to syphilis tell us to beware when using the arsenicals in such cases. In our experience we have never encountered a single instance of having to suspend this drug on account of cardiac symptoms. Only three deaths¹ in patients over six months of age have

occurred in more than two thousand cases that have been treated in my clinics. Autopsy on two of these showed no cardiac abnormality, and the other child showed no evidence of a cardiac death.

Eight cases of our series showed organic heart disease. Three of these, four months, eleven months, and twenty-six months of age, respectively, had congenital heart lesions; two probably pulmonic stenosis, and the youngest probably a patent ductus arteriosus. All three had 4+ Wassermanns and came from families with definite syphilis. Whether congenital syphilis played a part in these cases is not known. Only autopsies would have revealed definite evidence. The other five

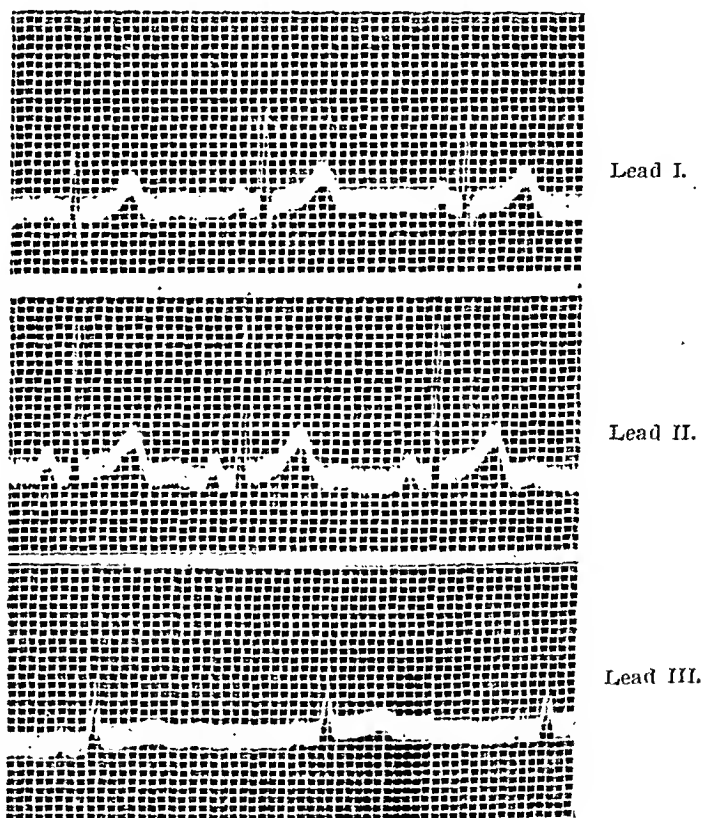


Fig. 1.

cases showed histories, symptoms, physical signs and other data which led to a diagnosis of mitral disease of a rheumatic nature. Three other congenital syphilitic children showed chorea but without positive heart findings. A nine-year-old boy with a 4+ Wassermann was diagnosed from eye findings and a blood pressure of 145/90 mm. as having juvenile arteriosclerosis. His heart was normal so far as physical signs, electrocardiogram and x-ray were concerned.

The only case with heart findings that might be classified as being due to congenital syphilis is that of an eight-year-old girl with active interstitial keratitis, with a 4+ Wassermann, and with a positive family history of syphilis. Her aortic second sound was very loud and

almost ringing in character at times. There was no murmur at the base but a definite systolic soft blow at the apex transmitted to the left anterior axillary line. X-ray showed no abnormality. The heart was not enlarged and caused her no embarrassment. The electrocardiogram (Fig. 1) shows no abnormality with the exception that the S-T interval comes off 1 mm. below the base line in Lead I and 1 mm. above the base line in Leads II and III.

COMMENT

Four hundred and seventeen cases of congenital syphilis ranging in age from three months to forty-two years were studied with reference to heart disease being caused by the *Spirocheta pallida*. Up to the present moment not one of the cases has shown signs or other collected data that would lead one to make a definite diagnosis of syphilitic heart disease.

REFERENCE

1. Givan, Thurman B.: Arsenical Reactions in Congenital Syphilis Complicated With Alkalosis, N. Y. State J. Med., 29: 132, 1929.

DISCUSSION

Dr. H. E. B. Pardee, New York, N. Y.—Although Dr. McCulloch* has not been able to present his paper today, I believe from my correspondence with him that he is able to report very much the same sort of findings as have been recorded by Dr. Givan and Dr. Previtali. He was not able to find an appreciable amount of cardiovascular disease in these children. In connection with this finding it must be remembered that these children represent a very different type of case from those which have been discussed here today, who are suffering from cardiovascular disease, and who apply for treatment. These children represent so many exposures to the infecting agent of syphilis, and it should not be expected that the incidence of cardiovascular involvement would be great. We do not know what percentage of adults infected with syphilis go on to develop lesions of the cardiovascular system. It is likely that only a small percentage does so, and so we should not be surprised if the amount of cardiovascular syphilis in children with hereditary infections is not great.

*McCulloch, Hugh: Congenital Syphilis as a Cause of Heart Disease, see p. 136.

CONGENITAL SYPHILIS AS A CAUSE OF HEART DISEASE*

HUGH McCULLOCH, M.D.†

SAINT LOUIS, Mo.

INTRODUCTION

IT IS known that syphilitic infection is followed in many instances by localization of the disease in the heart or large blood vessels of the human body. Even when the infection is recognized early and treated carefully, cardiac and vascular complications may occur five, ten or more years later in life; and in unrecognized or untreated cases, the frequency of these late lesions in the heart and blood vessels is known to increase. Just how probable the occurrence of syphilitic heart disease in a given individual will be, cannot be stated accurately. Conservative estimates would place the frequency at about 25 per cent in untreated cases and lower in well-treated cases. Since syphilitic infection of infants before birth from a syphilitic mother is a common disease and since the course of this type of syphilis is comparable in many ways to an infection acquired later in life, one would suspect that those children would frequently show signs of heart disease. A group of children with congenital syphilis has been studied to note whether or not this same tendency existed for the heart to become the seat of the disease following fetal infection. Many children are born while in the stage of infection which is comparable to the secondary stage of acquired syphilis, and a smaller number live to reach the stage comparable to tertiary syphilis of the adult.

LITERATURE

Interest in this study was increased by many reports in the literature on the probability of such an infection in fetal life resulting in heart disease both during childhood and also later in life. Warthin¹ has directed attention to the probability of sudden death from a latent syphilitic myocarditis, a type of lesion that is known to occur in children. Other acute infections in childhood, such as diphtheria, scarlet fever, and typhoid fever, are known to be followed by a myocarditis which may be the cause of sudden death in later life. Warthin also has well described the lesions to be found in the heart. He reported² twelve cases of congenital syphilis, nine occurring in infancy and early childhood, three in children after puberty all of whom showed the presence of the disease in heart muscle tissue. He was able to demonstrate the spirochete in the tissue even in the absence of histo-

*Read by title.

†From the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's Hospital.

logical lesions or spirochetes elsewhere in the body. In his description³ of the histological findings, he states that in every case he has found fatty degeneration of the heart muscle to be present either as a diffuse fatty change or as a focal process. He says that as far as the organism of syphilis is concerned, it may cause a focal or a more diffuse degeneration of the myocardium before any interstitial changes occur, a purely parenchymatous change in the heart muscle. This lesion may heal without an interstitial reaction or focal fibroid areas as well as focal calcification of the degenerated muscle fibers can follow the primary lesions of the myocardium. The latter process would constitute changes responsible for heart disease in later life. Three cases described in older children were examples of this. One case had a history of old cardiac disease without a rheumatic infection, the other two showed decided underdevelopment.

There are numerous reports of cases of heart disease occurring among congenital syphilitic children. Fournier⁴ has directed attention to the fact that various heart malformations may occur in subjects of hereditary syphilis. Case reports by Anderson⁵ and Neugebauer⁶ have been made. A collective review of cases with a report of an additional case has been made by Stobie.⁷ deStefano⁸ reports 32 cases of children with congenital malformations of the heart who were admitted to the Children's Clinic at Naples in the previous six years. Seventy-two per cent presented unmistakable signs of inherited syphilis and it was probable in all the others, except 5. His report does not include an examination of the heart muscle tissues for the presence of spirochetes or the histological changes of syphilis described by Warthin. The blood Wassermann test was positive in 27 of the 32 cases. Many of the heart malformations described were similar to those which may be found among children who do not have congenital syphilis; for example, patent foramen ovale, ductus arteriosus, or interventricular septum. Hahn⁹ discusses the relationship between congenital syphilis and heart disease in early life of 130 cases of congenital syphilis and syphilitic fetal injuries. A large number, 80 to 90 per cent, showed a pure mitral stenosis. He regards the stenosis as evidence of retarded growth of heart muscle tissue following the syphilitic infection. Subjective symptoms were very slight and decompensation was never observed unless the stability of the anatomical condition was disturbed by bacterial infection of the valve.

Fordyce¹⁰ describes 9 children with rheumatic heart disease who were also congenital syphilitics and in whom the striking feature was the absence of clinical signs pointing to the presence of a syphilitic infection. He suggests that an important subgroup of rheumatic children can be defined in whom the rheumatic infection is superimposed upon congenital syphilitic infection and undetected and untreated syphilis.

MATERIAL

The group of cases which forms the basis for this report has been seen in the Washington University Dispensary, the out-patient department of the St. Louis Children's Hospital. As a part of the general pediatric clinic, the syphilitic children and cardiac children are cared for as special groups. On admission each child first is seen in the general clinic when he receives a physical examination and is then referred to the special group for further care. While attending the syphilitic or cardiac clinic, the child is examined frequently and among other things, the presence of signs of syphilis and the Wassermann reaction being noted on all cardiac children and the presence of signs of heart disease on all syphilitic children. It was recognized that there were very few children who belonged to both groups so that the high incidence of heart disease among syphilitic adults did not seem apparent in children. The experience in this clinic has been sufficiently large now to warrant a report of the situation at the present time.

During the ten-year period beginning with 1915 and ending with the end of 1924, there have been in all 40,470 children treated in the general pediatric clinic. Children admitted after this period have not been included in this study, since it was felt that recent admissions would not have been under observation long enough. During this same period a diagnosis of congenital syphilis has been made on 939 of these children, or 2.3 per cent. This group of children was divided into two groups: those under two years of age, 441, and those over two years of age, 498. A diagnosis of structural heart disease has been made on 458 children during this same period, or 1.1 per cent. This number does not include children with chorea or with potential heart disease.

Of the 939 syphilitic children, 124 are known to be dead. Of this number 53 died in the Children's Hospital and autopsies were performed on a total of 34; two of these were above the age of two years and 32 under two years of age. Among the 34 autopsies, a syphilitic lesion of the heart was found on the following three children:

CASE 1.—H. H., Children's Hospital No. 9738, aged three months. Clinical diagnosis of congenital syphilis with no signs of heart disease. At autopsy there was found a fibrosed atrophy of the right ventricle, hypertrophy and dilatation of the right auricle with a patent foramen ovale and ductus arteriosus. There was evidence of syphilis on microscopic section of the heart muscle.

CASE 2.—L. H., Children's Hospital No. A-1049, aged four weeks. Clinical diagnosis of congenital syphilis. At autopsy, the heart muscle was very pale and much enlarged and the foramen ovale was wide open. There was marked thickening of the epicardium with newly formed fibrous tissue in which were enmeshed great numbers of large mononuclear and lymphocytic cells. The muscle bundles of the heart were all widely separated with thick bands of the same character of tissue; the blood vessels large and small showed a marked fibrosis, thickening of the walls, and there was wide constriction of the lumen. Levaditi stains showed spirochetes.

CASE 3.—D. L. R., Barnes Hospital No. 8001, aged three months. Clinical diagnosis of hereditary syphilis, bronchopneumonia, septicemia, pneumococcus type IV. Post-mortem examination revealed a heart which weighed thirty-four grams, the musculature appeared normal. Microscopically, the bundles of heart muscle fiber are separated by bands of new forming connective tissue which in some instances are as broad as are the bundles of muscle fibers. There is also a mononuclear reaction throughout the section, the cells being to a great extent of the large mononuclear type. The cells are seen both between the bundles of muscle fibers and between the separated fibers. There is seen a similar connective tissue and cell reaction about the vessels in this section. In some instances, this being a rather marked change.

No one of the other 29 children under two years of age who were examined at autopsy showed evidence of heart disease. All of the 32 children showed extensive syphilitic disease in other organs and spirochetes could be demonstrated in the affected tissue. The clinical course and post-mortem examination of these children indicated that they were suffering from a generalized syphilitic infection and that death was probably due to the toxemia associated with the infection. No one of this group who died or of the total group of 441 children under two years of age showed signs of congestive failure of the heart or other cardiac symptoms during life or associated with death. This group of children under two years of life corresponds then to the group of adults with generalized syphilitic invasion of the whole body during the so-called "second stage" of the disease following a primary infection.

Children with syphilitic infection who live past two years of life show signs of the disease in a somewhat different manner. The common physical signs in this age group are keratitis, characteristic (Hutchinsonian) caries of teeth, deafness, and interstitial changes in such structures as the brain, liver, and bones. They rarely suffer from any toxemia, do not become acutely ill from the syphilitic infection, and usually die of some intercurrent infection. Of these children who lived to be over two years of age, there were 498 in this study and of this number two, T. S., Children's Hospital No. 16341, and S. S., Children's Hospital No. 651, died of heart disease and three others who have not died are known to have heart disease. The two children who have died also had a very definite history of rheumatic fever, chronic tonsillitis, and physical signs of the type of heart disease usually seen in rheumatic children. It could not be determined that the presence of the syphilitic infection contributed to the fatal outcome of the heart disease. They both had clinical signs of the syphilitic infection other than the heart disease. Three of this group, R. W., Dispensary No. A-75048, O. G., Dispensary No. 37873, and A. P., Children's Hospital No. 18185, were alive when last heard from, the latter at the age of seventeen years. These three children gave no history of rheumatic

fever though such a condition could have existed, for the heart disease was of the type usually seen in rheumatic children. The last child, A. P., when last seen showed almost no signs of heart disease, though during the hospital admission she had an acute pericarditis, enlargement of the heart with mild congestive failure, and mitral valvular disease. She had no signs of syphilis other than a positive blood Wassermann reaction. This group of five cardiac children in a total number of 498 with congenital syphilis is about the same frequency as would be found in any normal control group. This 1.0 per cent frequency coincides with the 1.6 per cent frequency of the total of 458 children with heart disease who were found among the total of 49,470 children admitted to the general clinic during the ten-year period included in this study. They correspond to the group described by Fordyce.¹⁰

SUMMARY

Of 40,470 children under fifteen years of age admitted to the outpatient department of the St. Louis Children's Hospital, during a ten-year period from 1915 to 1924 inclusive, 939, 2.3 per cent, were found to have congenital syphilitic infection and 458 were found to have recognizable heart disease. Of the 939 children with syphilis, 441 were under two years of age. It was possible to obtain autopsies on 32 children who died at this age period and 3 showed the presence of syphilitic heart disease. No one of the other 29 who died, or 409 who lived, had symptoms at any time referable to heart disease.

Four hundred and ninety-eight of the syphilitic children were over two years of age and of this number, 5, or 1.0 per cent, were known to have heart disease. Two of these 5 died but without post-mortem examination and 3 were living when last heard from. The signs of heart disease in these 5 children were similar to those seen in children with rheumatic heart disease but without syphilitic infection. This frequency of 1.0 per cent coincides with the frequency of 458 children (1.1 per cent) with heart disease among the total of 40,470 children admitted to the general clinic, or in other statistical surveys of the incidence of heart disease among normal or control children.

No one of the children up to the age of fifteen years of life has died suddenly or showed signs of heart disease similar to syphilitic heart disease seen in adult or later life. The observations made on routine examination of this group of children were not done with the idea of proving the existence or nonexistence of a causal relationship between congenital syphilis and heart disease. The number included seems large enough to represent a satisfactory experience in a general Children's Clinic.

CONCLUSIONS

There is no evidence in this study that congenital syphilis contributes to the incidence of heart disease in children up to the age of fifteen years. That heart disease and sudden death may follow this type of infection later in life is not made clear by this study, but it may be supposed that instances of this sequel would be about equal to those that follow other acute infections of childhood.

REFERENCES

1. Warthin, A. S.: AM. HEART J. 5: 1, 1925.
2. Warthin, A. S.: Harvey Lecture, Am. J. M. Sc. 141: 398, 1911.
3. Warthin, A. S.: J. A. M. A. 58: 409, 1912.
4. Fournier: Gaz. Hebd. Paris 3: 1133, 1898.
5. Anderson: Lancet 1: 648, 1915.
6. Neugebauer: Wien. klin. Wchnschr. 28: 503, 1914.
7. Stobie: Quart. J. Med. 15: 26, 1921.
8. deStefano: Pediatrics 28: 992, 1920.
9. Hahn: Zentralbl. f. inn. Med. 42: 818, 1921.
10. Fordyce, A. D.: Brit. M. J. 1: 530, 1930.

gurgitation; nine, or 40 per cent, were temporarily improved. Three were classed as myoeardial or coronary syphilis; only one showed improvement. Fifty of the entire group of eighty-eight patients were clinically improved; twenty-eight, or 31 per cent, were not influenced by the drug. The patients studied were judged improved, stationary or worse by comparing the symptoms and findings before and after neoarsphenamine treatment. The effect on the prominent symptoms is analyzed in Table II. It shows: Pain a complaint by forty-four patients, relieved in twenty-five, unchanged in fourteen, and aggravated in five; dyspnea a complaint in forty-eight, improved in twenty-eight, unchanged in thirteen, aggravated in seven; palpitation a complaint by twenty-four, relieved in thirteen, unchanged in seven and aggravated in four; murmurs present in seventy-five patients showed improvement in four, no change in sixty-three, aggravation in eight; urinary findings (albuminuria and casts) present in sixteen patients improved in eight, unchanged in six and aggravated in two. The Wassermann reaction, positive at the start of treatment in eighty-five patients, was rendered negative in twenty-three patients, became less strongly positive in three and was uninfluenced by the treatment in sixty-two.

TABLE II

| | PAIN | DYSPNEA | PALPITA- TION | MURMURS | URINARY FINDINGS | EDEMA | COUGH |
|-----------------------------|------|---------|------------------|---------|---------------------|-------|-------|
| Total cases with symptom | 44 | 48 | 24 | 75 | 16 | 17 | 15 |
| Relieved or improved | 25 | 28 | 13 | 4 | 8 | 9 | 6 |
| No effect | 14 | 13 | 7 | 63 | 6 | 5 | 5 |
| Aggravated | 5 | 7 | 4 | 8 | 2 | 3 | 4 |

As mentioned previously, the symptomatic improvement was temporary. The average period of relief was about fourteen months, varying from two months to five years.

The recorded improvement in murmurs of four patients was a lessened intensity of basal murmurs in two and a disappearance of aortic diastolic murmurs in two. The latter interesting observation, occurring in two decompensated patients after compensation had been established, can best be explained by attributing the murmur to a relaxed aortic ring. With compensation established, the tone of the aortic ring is improved, and the regurgitant murmur disappears.

The improvement in urinary findings coincided with the improvement in edema and probably indicated that the albuminuria was due to renal passive congestion.

The table records ten patients who became symptomatically worse. In three there is evidence of actual anatomical damage by neoarsphen-

amine. The kidneys of one patient, whose case is cited later, were probably damaged. Another case, also described in detail, showed marked increase in signs of aortic insufficiency. Another patient developed acute red atrophy of the liver and died. No cases of sudden death or aneurysmal rupture were observed.

CASES TO ILLUSTRATE HARMFUL EFFECTS

CASE 1.—L. O., colored man, forty-one years old, referred to cardiac clinic Nov. 28, 1924, from an industrial plant, because the company physician had discovered a murmur. In December, 1922, an examination by the same physician had revealed no heart abnormalities. He had no complaint except weight loss of ten pounds in three months. Examination revealed the heart enlarged to the left (14.5 cm.) in the sixth interspace, a distant diastolic murmur over aortic area, positive Duroziez's sign, systolic blood pressure 118 mm., diastolic 70, Wassermann three plus and x-ray evidence of aneurysm of aorta. Mercurial rubs and iodides were administered from December 1 to December 28. Then he received three doses of neoarsphenamine (0.3 gm.) at weekly intervals. After the third dose, the diastolic murmur became definitely more harsh, the blood pressure changed to 120/60 mm., and slight substernal distress was noted. Neoarsphenamine was then discontinued because it was felt that the organic changes were progressing in spite of treatment and perhaps were aggravated by the treatment.

CASE 2.—E. L., colored, forty-five years old, who previously had generalized anasarca, presumably the result of heart failure, was given 0.3 gm. neoarsphenamine on November 28, 1929, after a preliminary course of mercury and iodides. Prior to the injection there were no urinary findings, and blood pressure was 110/60 mm. Two days later edema of the ankles and eyelids developed, and albuminuria and urinary casts were found. Edema soon became generalized and persistent. The blood pressure rose to 160/100. The nephritis persisted for three months.

CASES TO ILLUSTRATE TEMPORARY CLINICAL IMPROVEMENT

CASE 3.—A. T., white, laundryman, aged fifty years, when first observed August 30, 1926, complained of severe boring substernal pain, dyspnea and palpitation. Examination revealed an enormous aneurysm of the arch and of the descending aorta (x-ray). The heart was not enlarged; the tones were clear except for a soft systolic murmur at the base. Iodide, mercury and analgesic drugs were used for ten weeks, and there was no relief from the severe pain. Striking pain relief was noted the day after one dose of neoarsphenamine was given. He remained in relative comfort for nine months, receiving during this period twenty-four injections of neoarsphenamine (0.3 gm.). During this period he received also potassium iodide. The final outcome of this case is unknown because the patient left the city.

CASE 4.—J. D., a white male, sixty years old, entered the clinic October 12, 1928, complaining of dyspnea, cough, and generalized edema. Asthmatic attacks had been present for a year, dyspnea and edema for three months. Gonorrhea and syphilis were acquired sixteen years before. Examination revealed a man acutely ill, with labored breathing, blood pressure 180/110 mm., generalized soft edema, huge heart with marked increase of mediastinal dullness, systolic and diastolic murmurs over the aortic valve, pulsating palpable aneurysm of the right carotid artery and four plus blood Wassermann. He was sent to Wesley Memorial Hospital where he remained until January 30, 1929. On discharge he had no dyspnea, pain, or edema. While in the hospital, the treatment consisted of digitalization, a course of iodide and mercury followed by weekly injections of neoarsphenamine, which were

continued until July 15, 1929. About three months after the treatment was started, the diastolic murmur disappeared. On July 25 the Wassermann was negative. In September, 1929, dyspnea, cough and pain developed but were relieved when he returned to the hospital. In January, 1930, after another series of neoarsphenamine treatment the Wassermann had become four plus. Symptoms of decompensation recurred February 7, 1930, and became worse until death on March 5, 1930. This case illustrates the symptomatic improvement which occurred in a man who received neoarsphenamine while suffering from cardiac decompensation. Although the improvement was temporary, we believe that the use of the drug in this case, as in others, caused some prolongation of life.

SUMMARY

A clinical study on the effect of neoarsphenamine on the symptoms of patients with cardiovascular syphilis is presented. Symptomatic improvement is believed to be a neoarsphenamine effect in 57 per cent of the cases. Twelve per cent showed aggravation of symptoms; probable anatomical damage was produced in three patients. No cases of sudden death or aneurysmal rupture were noted. A higher percentage of improvement is noted in patients who have syphilitic aortitis without definite aneurysm or aortic regurgitation. If the drug is cautiously administered in small doses, patients functionally classed 2 b (American Heart Association) may be benefited by the drug.

Improvement in the serological reactions of the blood does not always parallel the symptomatic improvement. Although the lives of patients with cardiovascular syphilis are perhaps prolonged by neoarsphenamine treatment, there is no evidence in any case studied which shows that the disease was permanently arrested.

DISCUSSION

Dr. Alexander Lambert, New York, N. Y.—When salvarsan first came out, a full dose used to be given to the syphilitic individual with cardiac disease or with aneurysm. These patients did well for about six weeks. Then we saw cases where the patient suddenly dropped dead without warning. The effect had been that of degeneration of the wall of the aneurysm. After that we never gave a dose of more than 0.1 gram, and always accompanied with mercury and iodide. Salvarsan was given once a week, and in that way there were not so many accidents. The patients were usually distinctly improved, but there were other cases that did not improve. It must be emphasized that the amount should never exceed a small dose given at five or six-day intervals. The drug does stop pain more quickly than any other thing in syphilitic aneurysm.

Dr. F. N. Wilson, Ann Arbor, Mich.—I have seen two or three patients with luetic heart disease in whom arsphenamine therapy was promptly followed by striking changes in the electrocardiogram. These changes were either permanent or persisted over a long period.

Dr. Norris, Springfield, Ill.—In the patients with some degree of heart failure, and treated with arsphenamine, what was the duration of life subsequent to treatment?

Dr. A. G. Sullivan, Hot Springs National Park, Ark.—Preliminary treatment should be stressed, as it is a very important factor. In the U. S. Public Health Service Clinic at Hot Springs a routine treatment is used consisting of three intra-

muscular injections of mercury and two injections of salvarsan weekly. We find that as a result of routine treatment (without careful cardiac examination) we had several deaths attributable to salvarsan. Autopsy showed scar tissue formation around the coronary openings. As a result we gave to our cardiac patients considerable preparatory treatment (at least a month) with mercury and iodides before starting salvarsan in small weekly doses, and since then we have had no deaths attributable to the treatment. In judging the length of preparatory treatment, cases already showing some interference with intraventricular conduction by slurring, notching or widening of the QRS complex should have more preliminary treatment. Unfortunately, mercury and iodides alone will not stop the progress of aortitis. Something more has to be done. In those cases which we feel are not suitable risks for salvarsan we are using bismuth. Its exact value in the treatment of cardiovascular syphilis is still undetermined.

Dr. W. H. Robey, Boston, Mass.—I thoroughly appreciate what Dr. Sullivan said. Whether there is much cardiovascular disease or not, if a middle-aged patient has syphilis, the physician should proceed with caution.

Dr. Hines (closing).—Electrocardiograms were made at the time of first admission to the clinic. No analysis was made of this work. In patients who were edematous the period of improvement was short. One man remained well a year. That was the longest period of relief noted in this group. Mercury and iodide were used before arsphenamine was started.

THE TREATMENT OF CARDIOVASCULAR SYPHILIS

A STUDY OF THE DURATION OF LIFE IN 141 TREATED AND UNTREATED PATIENTS WITH AORTIC REGURGITATION AND AORTIC ANEURYSM*†

JOSEPH EARLE MOORE, M.D., AND JAMES H. DANGLADE, M.D.
BALTIMORE, MD.

THE treatment of cardiovascular syphilis is a controversial subject on which there are as yet wide differences of opinion, ranging from deepest pessimism to unbounded optimism. One school of thought holds that treatment should be limited to such medical measures as rest, restriction of activities, diet, and digitalis, and that if antisyphilitic treatment is given at all, it should be confined to the iodides and mercury by mouth or by injection. The opposite viewpoint is held by others who, while conceding the value of conservative treatment, nevertheless feel that the arsenicals and bismuth may be added to the treatment armamentarium without risk and with marked benefit. The literature upholding one or other of these points of view is voluminous, but is based almost entirely on impression or opinion, much of which is unconvincing to the skeptic. We are unable to find adequate reports appearing since the introduction of modern methods of syphilotherapy, which deal with the question of the possible prolongation of life in a series of treated as compared with a series of untreated patients with cardiovascular syphilis. We shall attempt to supply this deficiency, limiting the discussion of our material to this major point, and, owing to the limitations of time and space, avoiding a discussion of the literature, which will be considered in some detail in a subsequent communication.

THE MATERIAL OF THIS STUDY

The primary interest of the syphilologist, so far as cardiovascular syphilis is concerned, lies in the question of early diagnosis and, by means of adequate treatment, the prophylaxis of its later manifestations. For this reason he is particularly prone to make the diagnosis of syphilitic aortitis on the basis of symptoms (substernal pain or oppression, paroxysmal dyspnea), with physical findings (increased retrosternal dullness, accentuated ringing aortic second sound in the absence of hypertension, etc.), and teleroentgenographic evidence of a widened inelastic aorta, in the absence of any valvular insufficiency. He is supported in this attitude by the great frequency of aortic lesions

*From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital.

†This investigation has been supported by a grant from the Committee on Research in Syphilis, Inc.

at necropsy in syphilitic patients, so that the presumptive diagnosis is more often right than wrong. However, it is also true that aortitis diagnosed during life is often absent at necropsy; and this experience is so frequent that many internists are unwilling to accept the clinical diagnosis of syphilitic aortitis unless the patient has a definite aortic regurgitation or an aneurysm. The clinical differentiation of syphilitic myocarditis as an isolated lesion from other diagnostic possibilities is also extremely difficult. In order to avoid introducing any material which might be objectionable on the score of inaccurate diagnosis, we have therefore limited this study to patients with syphilitic aortic insufficiency and aortic aneurysm.

The files of the Syphilis Clinic contain the records of 222 patients with aortic regurgitation and 93 with aneurysm. These patients have been followed as carefully as possible by social service visits, search of the in-patient hospital records of the Johns Hopkins Hospital and six other hospitals in Baltimore, and an examination of the death certificates in the Baltimore City Health Department. As a result of this effort, it has so far been possible to trace the ultimate outcome in 90 patients with aortic regurgitation and 43 with aneurysm. The study is still in progress, and these numbers will be augmented in a subsequent communication. To the former group have been added 3 patients with syphilitic aortitis, 3 with syphilitic myocarditis, and 2 with angina pectoris; in all of whom the diagnosis is sufficiently clear cut to be above criticism. A total of 141 patients is thus available for discussion.

TREATMENT METHODS

So far as antisyphilitic treatment is concerned, we have ourselves undergone several changes of attitude. Ten or fifteen years ago, in the relatively early days of arsphenamine, this drug was given to ambulatory patients with cardiovascular syphilis with as much freedom as to other patients with less serious late syphilis. The result of this was a series of four or five immediate deaths on the treatment table, a few instances of sudden death within twenty-four or forty-eight hours (Herxheimer reaction), and a few instances of the sudden precipitation of congestive failure in patients whose compensation had been adequate prior to treatment. Unfortunately the records of many of these older patients have now been lost, so that accurate figures as to the incidence of these untoward accidents cannot be given. Since it was obvious that arsphenamine in average therapeutic dosage could not be given to ambulatory patients without grave risk, this form of treatment was discontinued, and for a period of two or three years our original therapeutic optimism was replaced by an even deeper pessimism. During this period (roughly 1921 to 1923) no treatment except the usual medical measures was employed. Patients seen during these years constitute a large portion of our control untreated material.

With the introduction of bismuth and the gradual recognition of the importance of the therapeutic paradox,* so well emphasized by Wile, the whole question of the treatment of cardiovascular syphilis was reapproached with caution, and with the accumulation of experience our present very elastic system was evolved. The method is not original with us, since other observers, notably Brooks, Schottmüller, Stokes, and Wile have arrived at approximately the same conclusions.

Making all allowances for the fact that the treatment of cardiovascular syphilis is a problem which differs with the individual status of every patient, and which cannot be systematized as can, for example, the treatment of early syphilis, our present scheme is about as follows: if the patient is admitted with congestive heart failure or if he has pronounced pain or frequent attacks of paroxysmal dyspnea without failure, he is placed at rest in bed as promptly as possible. The usual measures are carried out until compensation is regained, when treatment for syphilis is cautiously begun. Both the danger of therapeutic shock (Herxheimer reaction) and that of precipitating decompensation by the too rapid resolution of syphilitic inflammatory tissue (the therapeutic paradox) weigh against the initial use of any of the arsphenamine products. Treatment is started, therefore, with bismuth (or mercury) and potassium iodide. This is continued for at least ten to twelve weeks before any arsenical drug is used, and indeed whether or not an arsenical is ever employed depends largely upon the degree of cardiac reserve which the patient seems capable of accumulating. If this appears adequate, arsenical treatment is started after about three months of preparatory treatment, the drugs of choice being neoarsphenamine or bismarsen (bismuth arsphenamine sulphate given intramuscularly). The dose of each is small, never exceeding 0.45 gram of neoarsphenamine, usually 0.1 to 0.3 gram at weekly intervals. Courses are long, 10 to 12 injections to a course. Treatment is continuous, courses of neoarsphenamine alternating with courses of bismuth and the iodides, and is kept up for a minimum period of two years, and often indefinitely. It is desirable to avoid treatment reactions of any sort.

RESULTS OF TREATMENT

A study of these 141 patients provides many data of interest and importance, consideration of which must be deferred for a more detailed report. Here we are concerned only with the major question of prolongation of life as a result of treatment. Our results are pre-

*As defined by Wile (The Treatment of the Syphilitic Liver and Heart, A Therapeutic Paradox, *Am. J. M. Sc.*, 164: 415, 1922), this consists in a remarkable general improvement following arsenical treatment, followed in some cases by a most rapid deterioration with accentuation of the original cardiac defect. Two factors are suggested as explanations: "first that the syphilitic products have been too rapidly replaced by scar tissue, or second, that their rapid disintegration has produced a chemical change deleterious in its effect on the local lesion. . . . We are confronted with the remarkable paradox that the patient gets well or better of his syphilis and may die as the result of the dispersion of his syphilitic cardiac lesion."

sented in tabular form and need little comment. Not a single patient in the whole series had received any antisyphilitic treatment for the cardiovascular lesion before admission, so that the results are based on treatment given under our own observation.

TABLE I

THE EFFECT OF TREATMENT ON THE PROLONGATION OF LIFE IN ANEURYSM OF THE AORTA

| TREATMENT | TOTAL CASES | LIVING | DEAD | DURATION OF LIFE UNTIL DEATH OR LAST OBSERVATION, MEASURING FROM | |
|--|-------------|--------|------|--|--------------------|
| | | | | ONSET OF SYMPTOMS | START OF TREATMENT |
| None or very little | 11 | 0 | 11 | 9 months | 6 months |
| Equivalent of one course of an arsenical or one long course of a heavy metal (1½-3 months) | 12 | 8 | 4 | 34 months | 28 months |
| Equivalent of one long course each of an arsenical and a heavy metal (3-12 months) | 8 | 6 | 2 | 28 months | 43 months* |
| More than one year of adequate treatment | 12 | 7 | 5 | 69 months | 55 months |

In this group there were five patients whose aortic aneurysms were discovered in the course of routine physical examination (confirmed in each case by roentgenographic and fluoroscope examinations), the patients having suffered no symptoms referable to the aneurysm.

In Table I appear the figures as to the ultimate outcome and the duration of life in 43 patients with aortic aneurysm who received varying amounts of treatment. On the basis of the amount of treatment given the patients are divided into four groups: those who got none or very little (one or two injections of an arsphenamine product, or three or four injections of bismuth, or less than a month of mercury by inunction); those who were treated from six to twelve weeks (the equivalent of one arsenical course or one long course of a heavy metal); those treated from three to twelve months (roughly, the equivalent of a long course of an arsenical plus a long course of a heavy metal); and those treated for more than a year. In this and subsequent tables, only those patients are included who (a) are known to be dead or (b) are now in active attendance at the clinic, excepting in this group only one patient who was followed over eleven years but has not been seen for the last eighteen months. It is obvious at once that antisyphilitic treatment does accomplish something in the prolongation of life since, to compare the two extremes, all eleven patients who received no treatment are dead in an average period of nine months from the onset of symptoms; while of those "adequately" treated, 7 of 12 are still alive and the average period from onset of symptoms to death or the present is sixty-nine months.

Such a tabulation is always open to the criticism that the material of the various groups is not strictly comparable, that the lesion in the

untreated group was more serious or more rapidly progressive than in the treated. To judge of the seriousness of cardiovascular syphilis is largely to deal in intangibles, but one can at least summarize the material on the basis of the duration of symptoms and the incidence of congestive cardiac failure prior to the starting of treatment. These data appear in Table II. In the third vertical column is shown the number of patients in whom the aneurysm was discovered at the routine admission physical examination (always confirmed by fluoroscopy), though the patient had as yet suffered no symptoms from its presence. The presence or absence of congestive heart failure, both before and after the start of treatment, is also shown. The fact that in the well treated group symptoms before treatment had existed for an average of eighteen months as compared with an average of six months in each of the other groups, indicates that we have not selected unusually favorable cases for treatment.

We have repeatedly been impressed with the fact that many patients who received only a small amount of treatment failed to return for more because such complete symptomatic relief was obtained that the patient thought he was well.

TABLE II

THE RELATIONSHIP OF THE DURATION OF SYMPTOMS AND OF CARDIAC FAILURE TO THE OUTCOME OF TREATMENT IN ANEURYSM

| TREATMENT GROUP | TOTAL CASES | AVERAGE DURATION OF SYMPTOMS BEFORE TREATMENT | PATIENTS SYMPTOM-LESS BEFORE TREATMENT | CARDIAC FAILURE | |
|--|-------------|---|--|------------------|------------------------------|
| | | | | BEFORE TREATMENT | AFTER TREATMENT |
| None or very little | 11 | 6 months | 0 | 6 | 4 (in 6 cases no data) |
| Equivalent of one course of an arsenical or one long course of a heavy metal (1½-3 months) | 12 | 6 months | 2 | 3 | 3 (in 6 cases no data) |
| Equivalent of one long course each of an arsenical and a heavy metal (3-12 months) | 8 | 6 months | 5 | 0 | 2 (in 2 cases no data) |
| More than one year of adequate treatment | 12 | 18 months | 1 | 3 | 3 (in 1 case no data) |

The effect of treatment on the prolongation of life in 98 patients with syphilitic aortic insufficiency (including the 8 miscellaneous patients mentioned above) is shown in Table III.* In this group, the larger number of patients permits a further subdivision on the basis

*Of the 45 living patients in this group, all except 3 are still under observation or treatment. These three were observed for four, six and eight years, respectively.

of the amount of treatment given than in the aneurysm group. Here also the same favorable trend is apparent. For example, of 25 patients not given antisyphilitic treatment, 20 are dead and the average duration of life from the onset of symptoms to death or the present time (if living) is thirty-two months. At the other extreme, of 20 patients receiving more than one year of treatment, all are still living, at an average interval of sixty-five months from the onset of symptoms.

TABLE III

THE EFFECT OF TREATMENT ON THE PROLONGATION OF LIFE IN SYPHILITIC AORTIC INSUFFICIENCY*

| TREATMENT | TOTAL CASES | LIVING | DEAD | DURATION OF LIFE UNTIL DEATH OR LAST OBSERVATION, MEASURING FROM | |
|--|-------------|--------|------|--|--------------------|
| | | | | ONSET OF SYMPTOMS | START OF TREATMENT |
| None or very little | 25 | 5 | 20 | 32 months | 31 months |
| Equivalent of one short course of an arsenical or one long course of a heavy metal (1½-3 months) | 32 | 7 | 25 | 29 months | 20 months |
| Equivalent of two arsenical courses plus a heavy metal (3-6 months) | 10 | 5 | 5 | 34 months | 31 months |
| Equivalent of 3 arsenical courses (6-12 months) | 11 | 8 | 3 | 54 months | 37 months |
| More than one year of adequate treatment | 20 | 20 | — | 65 months | 58 months |

*Including 90 patients with aortic regurgitation, 3 with syphilitic myocarditis, 3 with syphilitic aortitis, and 2 with angina pectoris.

TABLE IV

THE RELATIONSHIP OF THE DURATION OF CARDIAC SYMPTOMS AND OF CARDIAC FAILURE TO THE OUTCOME OF TREATMENT IN AORTIC INSUFFICIENCY

| TREATMENT GROUP | TOTAL CASES | AVERAGE DURATION OF SYMPTOMS BEFORE TREATMENT | PATIENTS SYMPTOM-LESS BEFORE TREATMENT | CARDIAC FAILURE | |
|--|-------------|---|--|------------------|-----------------------------|
| | | | | BEFORE TREATMENT | AFTER TREATMENT |
| None or very little | 25 | 7 months | 1 | 17 | 9 (in 16 cases, no data) |
| Equivalent of one short course of an arsenical or one long course of a heavy metal (1½-3 months) | 32 | 10 months | 3 | 17 | 17 (in 8 cases, no data) |
| Equivalent of two arsenical courses plus a heavy metal (3-6 months) | 10 | 3 months | 1 | 4 | 4 (in 1 case, no data) |
| Equivalent of 3 arsenical courses (6-12 months) | 11 | 15 months | 0 | 5 | 7 (in 2 cases, no data) |
| More than one year of adequate treatment | 20 | 13 months | 5 | 3 | 1 |

In these patients it is much more difficult to decide the question of the comparable severity of the lesion in the different treatment groups. An attempt is made in Table IV, on the same basis as in the aneurysm group. Here an outstanding point is that the ultimate outcome is unfavorably influenced by the occurrence of congestive failure before treatment is started, although even a severe degree of failure does not necessarily preclude a favorable outcome. It will be noted that in 5 of 20 patients in the well-treated group, the aortic regurgitation was discovered at the admission physical examination, though as yet the patients had suffered no symptoms from its presence. In the remaining 15, however, symptoms had been present for an average of thirteen months before treatment was started, a period longer than in the least adequately treated groups; and three of the well-treated patients had had pronounced congestive heart failure before treatment.

TABLE V

THE AVERAGE DURATION OF LIFE IN TREATED PATIENTS WITH AORTIC INSUFFICIENCY

| TREATMENT GROUP | TOTAL CASES | PATIENTS LIVING | AVERAGE DURATION OF LIFE FROM | | PATIENTS DEAD | AVERAGE DURATION OF LIFE FROM | |
|---|-------------|-----------------|-------------------------------|-----------------------------------|---------------|-------------------------------|---------------------------------|
| | | | ONSET OF SYMPTOMS | BEGINNING OF TREATMENT TO PRESENT | | ONSET OF SYMPTOMS TO DEATH | BEGINNING OF TREATMENT TO DEATH |
| None or very little | 25 | 5 | 52 mo. | ----- | 20 | 22 mo. | 21+ mo. |
| Equivalent of one short course of an arsenical or one long course of a heavy metal (1½-3 mo.) | 32 | 7 | 62 mo. | 49 mo. | 25 | 21 mo. | 12 mo. |
| Equivalent of two arsenical courses plus a heavy metal (3-6 months) | 10 | 5 | 48 mo. | 45 mo. | 5 | 20 mo. | 16 mo. |
| Equivalent of 3 arsenical courses (6-12 months) | 11 | 8 | 60 mo. | 41 mo. | 3 | 35 mo. | 28 mo. |
| More than one year of adequate treatment | 20 | 20 | 65 mo. | 58 mo. | - | - | - |

The question of duration of life in this group is further analyzed in Table V, in which are shown the figures for living and dead patients. The fact that 5 patients who received no treatment whatever are still living after an average period of fifty-two months illustrates the extreme difficulty of evaluating the effect of treatment in an individual patient. Had these 5 patients been treated, one would be tempted to regard them as therapeutic successes. The only fair method of approaching the problem, therefore, is to estimate averages in a large number of fairly comparable cases. When expressed as in this table, the results are less striking than when grouped as in Table III. The intangible

factor incapable of expression in figures is that of the 20 well-treated living patients; many more are partially or completely symptom free and able to do some form of work than those less adequately treated.

SUMMARY AND CONCLUSIONS

1. The treatment of cardiovascular syphilis is best accomplished by a combination of such routine medical measures as rest, restriction of activities, and digitalis together with antisyphilitic treatment.

2. An acceptable method of antisyphilitic treatment is based on the avoidance of therapeutic shock (the Herxheimer reaction) and the therapeutic paradox by starting treatment cautiously with bismuth or mercury and the iodides, by the use of long courses of small doses of neoarsphenamine or bismarsen, and by the prolongation of treatment for a minimum of two years with alternation of these drugs.

3. A study of 43 patients with aortic aneurysm demonstrates that life may be prolonged from an average of nine months from the onset of symptoms in untreated patients, to an average of sixty-nine months in patients receiving one year or more of such treatment.

4. A study of 90 patients with aortic regurgitation and 8 with various other forms of syphilitic cardiovascular disease shows that life may be prolonged from an average of thirty-two months from the onset of symptoms in untreated patients to an average of sixty-five months in patients receiving one year or more of such treatment.

5. These data seem to demonstrate that properly directed antisyphilitic treatment is of great value in cardiovascular syphilis.

DISCUSSION

Dr. Horine, Louisville, Ky.—This brings up an interesting point about which I would like to ask Dr. Danglede. He said the patients did not have aortic insufficiency but had cardiac enlargement. What produced the enlargement?

Dr. Alexander Lambert, New York, N. Y.—In looking back over the experience of thirty-six years at Bellevue Hospital we can feel a degree of satisfaction in that we can give a great deal of benefit to cardiovascular syphilitic cases if we persist in some form of mixed treatment. The trouble is that as soon as patients get better they get careless and drop all forms of treatment and of course they retrograde. The idea that cardiovascular syphilis cannot be treated successfully is erroneous. The old idea was right that cardiovascular syphilis was the one thing that could be treated by mercury. That is the experience of more than one generation.

Dr. Wm. D. Reid, Boston, Mass.—I analyzed the cases at the Massachusetts General Hospital. There were three groups: (1) in which there was only slight treatment, and in this the length of life averaged one year; (2) a group with moderate treatment which averaged three years; and (3) a group with early and prolonged treatment in which many of the patients were able to go back to full physical work, and life was prolonged.

Dr. E. P. Carter, Baltimore, Md.—This study has made very patent the fact that in certain conditions, with proper supervision and proper therapeutic care, we can accomplish a great deal in cardiovascular syphilis. The question of the subjective relief of symptoms has not been touched upon but the evidence seems to

support a view, which is rather against the impression of some of the men in syphilis clinics, that careful, systematic treatment of cardiovascular syphilis does add to the expectancy of life.

Dr. A. G. Sullivan, Hot Springs National Park, Ark.—It would seem almost impossible to make a diagnosis of syphilitic myocarditis. The myocardium is invaded by the spirochete, but it is extremely difficult to demonstrate clinically the signs and symptoms resulting from that invasion. They are probably due to interference with the coronary blood supply at the coronary openings in the aorta. Therefore, I was interested to know if these cases also had involvement of the aorta.

Dr. E. P. Carter, Baltimore, Md.—I have the impression that there are cases in which one is justified in interpreting the condition as diffuse myocardial disease. I do not believe, however, that all round-celled infiltration is syphilis of the myocardium. We have had 5 cases of individuals between thirty and forty years of age, with marked cardiac failure, watched over a long period, and coming to autopsy with characteristic periarterial focal infiltration regarded by the pathologist as indicating the result of syphilitic change. One case had an acute pericarditis without endocardial disease. There were two cases of early luetic aortitis. The other had true involvement of the aorta. We have no justification for a positive statement that these lesions found histologically are due to the syphilitic virus. It is merely inference. We are not able to find the spirochetes.

Dr. Danglede (closing).—These patients had cardiac enlargement without aortic insufficiency at the original examination. None of them had arterial hypertension. The only explanation I can think of is that the syphilitic process in the myocardium produced weakness with resulting dilatation. One patient came back nine months later much improved by treatment. The cardiac outlines were reduced, and at that time there was a very soft diastolic murmur in the aortic area.

In the three cases mentioned we noted enlarged cardiac outlines (confirmed by x-ray) with widening of the aortic shadow but without aortic insufficiency. Their symptoms were those of myocardial failure, i.e., dyspnea, cyanosis, and dependent edema. There was nothing about the electrocardiogram that was conclusive at all. All had positive serology. We followed them up for from two to fifteen months after leaving the hospital. The diagnosis of syphilitic myocarditis was made after prolonged observation and largely by exclusion. Treatment was started cautiously. The end-results were very striking. Patients came around very slowly, but definite improvement was evident. All three patients mentioned are alive and are maintaining their improved condition.

We have repeatedly been impressed by the fact that patients lapsed from treatment because their symptoms were so promptly relieved. They considered themselves cured, only to return to the clinic anywhere from six to twenty-four months later because of the return of symptoms.

Dr. Moore (closing).—The most important thing in the discussion is really repetition. Dr. Wile made the statement four or five years ago that treatment of cardiovascular syphilis in the prearsphenamine days was satisfactory. Then salvarsan was introduced and used with misguided enthusiasm. I was one who made mistakes. The generation growing up now is impressed with the amount of harm that was done, and some of them have returned to treatment consisting of nothing but rest and digitalis. I think it is clear that if we revise our methods of treatment and include the use of antisiphilitic drugs with more caution, we shall get better results in the treatment of syphilitic cardiovascular disease.

PRINCIPLES UNDERLYING THE TREATMENT OF CARDIOVASCULAR SYPHILIS*

UDO J. WILE, M.D.

ANN ARBOR, MICH.

IT IS not only difficult but may be said to be hazardous to lay down axiomatic rules governing the treatment of a syphilitic individual. In no disease of human pathology does the individual enter so largely into the treatment of his case as occurs in syphilis. Age, duration of infection, previous treatment, coincident disease of other nature, social status, weight, and musculature are considerations of greatest importance which must be weighed in every case. However important these desiderata are in treating the patient with early diffuse syphilis, individualization becomes increasingly so when some particular system of the body presents itself as a therapeutic problem due to syphilitic late changes. In discussing the treatment of syphilitic heart disease, therefore, it is possible to lay down only the general principles which might govern the therapeutic procedures and to conform to the excellent general rule that each case in the last analysis presents its individual therapeutic problem.

From the clinico-pathological standpoint, we might first discuss the rare types of syphilitic heart disease which occur early in the course of syphilis. These represent a relatively small, little recognized, and unimportant group. The changes that occur later in the heart and great vessels make up a very large part of the clinical pathology of late syphilitic disease and present the most frequent and most serious of the syphilitic visceropathies. In the late group again we must distinguish those in which syphilitic disease is still active and those cases in which we are dealing with the mechanical end-results of a condition which, while it may progress, does so by degenerative changes rather than by further inroads of the disease itself. In the early group are a few cases of myocardial involvement coincident with or following shortly after the exanthematous period. These are ordinarily ascribed to widespread invasion of the spirochete into the myocardium and consequent early degenerative changes. Occasional sudden death from failure is recorded in this group, and not infrequent attacks of syncope, of heart-block, and of angina-like attacks. In view of the paucity of cases of this kind, and of the meager observations in the literature, it is not possible to lay down adequate criteria for their treatment.

*Studies and contributions of the Department of Dermatology and Syphilology of the University of Michigan Medical School, service of Dr. Udo J. Wile.

In a very small number of personal observations in which arrhythmia, tachycardia, heart-block, and sudden attacks of syncope have occurred, I have been impressed by the fact that this group responded well to energetic treatment in which the heavy metals have formed the background and in which the arsphenamines have been used sparingly. The relative infrequency of this group makes it seem quite possible that as occurs in other viscera, particularly the liver and kidneys, we may be dealing with subclinical heart involvement due to other causes in which the added insult of spirochetal invasion brings the picture into the foreground.

In the later cases, we must distinguish as particular therapeutic problems the following groups:

1. Energetically treated asymptomatic cases.
2. Energetically treated cases in which cardiovascular dysfunction exists.
3. Inadequately treated asymptomatic cases.
4. Inadequately treated cases with cardiovascular dysfunction.

To these four groups I would add a fifth in which cardiovascular disease, symptomatic or asymptomatic, may exist with other clinically predominant syphilitic visceropathies.

Broadly speaking, Group I represents a type of case in which it is frequently wise even in the presence of serologic evidence to withhold all treatment. Included here, the well compensated cases of aortic regurgitation are by far the most numerous, although included in it are also a few cases of subclinical aortitis and diffuse aortic dilatation.

From a rather wide experience with cases of these types, I have seen many endlessly and futilely treated in the effort to reverse a biological test. The continuous barrage of treatment in patients of this sort who have already had a good or fair background of therapy, in whom adequate compensation for their lesions exists, constitutes in my opinion a class in which more harm than good may be done by energetic anti-syphilitic treatment.

In the second group, that is, those energetically treated before the onset of cardiac disease, in which dysfunction exists, I would go further and state that during the stages of decompensation these cases should seldom if ever be treated as syphilis. The therapeutic problem is one of heart failure and the problem is a mechanical defect existing in a degenerated structure. Mercury, bismuth or arsphenamines are of no benefit, and in the presence of edema are definitely contraindicated.

In Group III, cases inadequately treated early, and with asymptomatic cardiovascular disease, much I think may be accomplished by judicious antisiphilitic treatment. To what extent we slow up or

inhibit the progress of such cases or keep them asymptomatic is difficult to determine. No one who ever has seen such cases in large number can fail to be impressed with the fact that many of them remain in a status quo, their physical signs remain, though occasionally even changes for the better are noted, and cardiac dysfunction is definitely postponed for them. Not a small part of their improvement must of course be due to the dispersion of syphilitic residua in other organs of the body, as well as in the bone marrow, spleen, and lymphoid tissues. The presence and persistence of such foci remote from the heart itself must also be recognized as contributory factors in the ultimate cardiac failure in untreated cases.

In the fourth group, inadequately or untreated cases in which cardiac dysfunction exists, we are faced with a very delicate therapeutic problem. These cases again should, I think, seldom if ever be treated for syphilitic disease during the stage of decompensation. After proper rest, digitalization, and other treatment resulting in the building up of their cardiac reserve, judicious treatment on conservative lines directed to the old syphilis is of unquestionable benefit.

Not only are the active foci in the heart itself, and the great vessels beneficially affected in this way, but the remote syphilitic lesions in other parts of the body with their contributory degenerating effects are dispersed.

Of particular importance, I think, at this point is the emphasis that the arsphenamines are not the drugs of choice. I am satisfied from a large number of observations that more harm than good is accomplished by the energetic antisymphilitic treatment of cases recovering from heart failure in this group. Absorption of syphilitic residua and replacement by fibrosis seem safer when slowly accomplished than when induced by energetic therapy. Iodide of potash and mercury or more lately bismuth in moderate doses have in my hands been happier choices than the arsenicals. This group in fact represents one of the few indications where ingested mercury or mixed treatment may judiciously be used, at least in the beginning.

Up to a few years ago, a series of experiences in which I had seen the use of the arsphenamines result in dysfunction and not infrequently in death led me to advise against them in any case of cardiovascular syphilis. However, with the introduction of tryparsamide into the treatment of neurosyphilis, I was early convinced of its great usefulness in certain cases of cardiovascular syphilis, especially in aortitis and in certain early aneurysmal dilatations. Perhaps from its extraordinary tonic effect, perhaps because of specific effect on the process itself, its judicious use is attended with a remarkable improvement in color, strength, and gain in weight so frequently as to merit a real place in the treatment of selected cases. As in the case of the other

arsenieals, however, it should never be used when decompensation is present or where this has already occurred.

The group of cases in which coronary disease is apparently present or suspected from the clinical picture are variously influenced by anti-syphilitic treatment. Some seem markedly benefited, others are not influenced and a third group is made definitely worse. My own experience has impressed me with the analogy of these cases to those of cerebral thrombosis. In this condition, the cases occurring relatively early in the disease, particularly in young persons, seem to be greatly benefited and many are arrested or cured by treatment. The later group and particularly older individuals respond less well.

The same seems to hold true with cases of apparent cardiac disease with associated anginoid pains. In both the cases of coronary disease and where angina pectoris as a syndrome is present, the best results are obtained by mercury, bismuth and iodide rather than by the arsphenamines.

Late cases of aneurysm with marked signs and symptoms have in my hands been disappointing in their response to antisyphilitic treatment. This failure to improve takes on added interest in the presence of response in the same patient to other syphilitic processes. I have on several occasions seen cutaneous gummas and syphilitic hepatitis completely relieved as symptom complexes in patients whose aneurysmal process was in nowise benefited.

SUMMARY

The treatment of the syphilitic heart disease is always a treatment of the individual patient. Such cases as are amenable to antisyphilitic régime respond well if not pushed too hard and if treated before decompensation has occurred or after it has been temporarily relieved. The mechanical end-results of syphilitic disease of cardiovascular nature are in no way influenced by antisyphilitic treatment. In those cases of cardiovascular syphilis in which benefit is achieved, this occurs not only because of dispersion of active processes in the affected part of the cardiovascular system, but in a large measure is due to the dispersion of remote foci elsewhere in the body.

Such foci in untreated cases must act as predisposing and contributory factors in the ultimate breakdown of the cardiovascular system. Fully compensated cases of cardiovascular syphilis which have a good background of early treatment are frequently cases which need not and should not be treated. Except for tryparsamide in certain selected cases of aortitis, better results are achieved by the conservative use of mercury, bismuth and iodide than by the arsphenamines. These comments are not intended as dogmatic, incontrovertible statements of fact, but are based entirely upon personal experience.

CLOSING DISCUSSION OF SYMPOSIUM

Dr. Haven Emerson, New York, N. Y.—One of the hazards of a symposium of this kind is that it forces authors into premature publicity. With rare exceptions the numbers of observations reported upon are so small as to forbid reliable use of the statistical method of presentation of results, as has been attempted here in several instances. In the great majority of the papers the correlations which are claimed are not significant, the probable error is of a high degree, and the conclusions are not statistically justified.

In using the mathematical expression of accumulated facts it is well to remember that comparability, objectivity, and reliability of the observed facts are of prime importance.

The statistical method may indicate the trend of facts toward certain conclusions. The critically controlled experiment is usually needed to give a conclusive answer to any question susceptible of scientific proof. The trend of many of the observations reported here today is indicated, but only by much more rigorous critical analysis can these be accepted as valid in view of the paucity of original data and the lack of controlled experiment.

Dr. Henson, St. Paul, Minn.—I think we would like to carry away with us a definite impression of the value of treatment in cardiovascular syphilis. As we listened to the various speakers, we note that they draw their material from different types of patients—from private practice, from hospitals, and from dispensaries. We are confronted by the fact that prognosis is influenced by the type of treatment and the type of lesion. Dr. Herrmann shows that his patients got treatment only for from ten days to two weeks on an average. Dr. Dauglade used mercury from three months up to sixty-five months. My own experience is in between these figures, and is drawn from both clinical and private practice. I use mercury for three months, then after a rest I give arsphenamine, 0.05 to 0.15, never giving more than 0.3 gm. I have 10 patients still alive six to ten years after beginning treatment.

Dr. S. R. Roberts, Atlanta, Ga.—As clinicians, and not statisticians, I think that the impression should go out that we need not be discouraged from drawing conclusions from cases. While statistics do show trends, we need not be too pessimistic. We do not have to wait for thousands of cases before publishing our results. After all, statistics are made up of the sum total of little things.

A preliminary note on "The Treatment of Syphilitic Aortic Regurgitation with Congestive Heart Failure," by Drs. George Herrmann and S. Chaille Jackson of New Orleans, La., was read by Dr. Herrmann. The complete report of this work will be published later.

The following papers were read at the meeting of the American Heart Association in Portland, Ore., July 9, 1929, and were published in full in the October, 1929, issue of the AMERICAN HEART JOURNAL.

SYPHILITIC CORONARY OCCLUSION IN AORTIC INSUFFICIENCY

J. H. CANNON, M.D.

CHARLESTON, S. C.

(Summary.) Two cases of syphilitic aortitis with insufficiency and occlusion of a main branch of a coronary artery are reported. The striking similarity of the cases is commented upon, and statistics from analysis of a small series of cases are utilized.

It would seem, therefore, that in young adults with syphilis and aortic insufficiency who do not exhibit the usual compensatory hypertrophy and whose progress is rapidly toward a fatal outcome, one may reasonably presume the involvement of one or more of the coronary openings in the syphilitic process.

ABNORMAL ELECTROCARDIOGRAMS IN PATIENTS WITH SYPHILITIC AORTITIS

IRVING R. JUSTER, M.D., AND HAROLD E. B. PARDEE, M.D.
NEW YORK, N. Y.

(Summary.) Of 50 patients with syphilitic aortitis who were studied, two-thirds had aortic insufficiency and one-third did not; about one-third had aneurysm; 5 had both aortic insufficiency and aneurysm.

In general the patients with aortic insufficiency were older than those without; shortness of breath was their chief complaint, though pain in the anterior chest was frequent, and almost one-third complained of edema. All but one showed a systolic murmur at the aortic area.

The electrocardiogram showed an abnormal T-wave in 85 per cent of these patients, and in 20 per cent it was of the coronary type. It was abnormal in only 38 per cent of those without the valve lesions and 1 case (7 per cent) showed a wave of the coronary type.

Ten autopsies were obtained on these 50 cases, and from a study of the autopsy material and the electrocardiographic records it appeared that the abnormality of the T-wave is probably due to encroachment upon the lumen of the coronary orifices by the syphilitic disease in the sinuses of Valsalva. The greater frequency of the T-wave changes in the group with aortic insufficiency is due to the fact that in these patients the aortitis involves the region of the valves near which the coronary arteries originate.

Changes in the T-wave of patients with syphilitic aortitis should be viewed as an indication of serious coronary involvement, but not necessarily as an indication of myocardial pathology.

This observation has an extremely important bearing upon our general understanding of the causes of abnormality of the T-wave.

The American Heart Journal

VOL. VI

DECEMBER, 1930

No. 2

Original Communications

THE RÔLE OF SYPHILIS IN THE ETIOLOGY OF ANGINA PECTORIS, CORONARY ARTERIOSCLEROSIS AND THROMBOSIS, AND OF SUDDEN CARDIAC DEATH*

ALDRED SCOTT WARTHIN, M.D.,
ANN ARBOR, MICH.

THE rôle played by syphilis in the etiology of angina pectoris, coronary sclerosis and thrombosis, and of cardiac infarction has never been clearly evaluated; and varying opinions have been held by clinicians as to its importance in the production of these conditions. The most recent writers, as Levine, believe that syphilis is rarely an underlying factor in the causation of coronary thrombosis. In only three of Levine's eighty-nine cases in which a Wassermann reaction was done was there a positive reaction, and in one other case with a negative reaction, there was a history of a primary infection. From this it would appear that only 4.5 per cent of his patients were syphilitic, and it does not necessarily follow that in these cases the syphilis was the etiologic factor in the production of coronary thrombosis. In one case only, a patient only thirty-six years old, the youngest in his series, did this seem likely. In the other cases the syphilis may well have been coincidental. Levine decides that coronary thrombosis and myocardial infarction are rarely caused by syphilis. However, in Levine's cases the diagnoses were chiefly clinical and gross pathological. In only forty-six of the cases were autopsies done, and the microscopic diagnosis of syphilis does not seem to have been considered. It is possible that microscopic criteria for the diagnosis of syphilis might have increased the percentage of syphilitics in his material. In thirteen autopsies on patients dying of coronary disease reported by W. J. Stone, microscopical examination showed syphilitic periarteritis in two cases. In eighty-six autopsies of coronary sclerosis, Willius and Brown found syphilis of the aorta in 19 per cent.

*Read before the Association of American Physicians, Atlantic City, May 6, 1930.
From the Department of Pathology, University of Michigan, Ann Arbor, Mich.

It was decided to approach the solution of this question from the standpoint of the microscopic diagnosis of syphilitic lesions, as this has never been carried out before on any large series of cases. In the twenty years, 1909 to 1929, there were in the Pathological Laboratory of the University of Michigan, 1675 autopsies on individuals over twenty-five years of age. Of this number, there were 408 males and 86 females that showed the microscopic lesions of active latent syphilis. These lesions consisted of characteristic perivascular infiltrations of lymphocytes and plasma cells around small vessels, with obliteration of the arterioles and resultant fibrosis. In about 50 per cent of cases the presence of *spirocheta pallida* was demonstrated in this lesion. The highest incidence of these lesions was found in the aorta; 97.6 per cent of cases for the first decade, 1909 to 1919; in 86.3 per cent of cases for the second decade, 1919 to 1929.

TABLE I*

| YEAR | TOTAL AUTOPSIES OVER 25 YEARS | MALES WITH LATENT SYPHILIS | FEMALES WITH LATENT SYPHILIS |
|------|----------------------------------|-------------------------------|---------------------------------|
| 1910 | 11 | 1 | 0 |
| 1911 | 20 | 3 | 1 |
| 1912 | 26 | 5 | 1 |
| 1913 | 24 | 8 | 3 |
| 1914 | 31 | 10 | 0 |
| 1915 | 35 | 17 | 4 |
| 1916 | 48 | 19 | 3 |
| 1917 | 90 | 36 | 9 |
| 1918 | 40 | 16 | 3 |
| 1919 | 61 | 20 | 3 |
| 1920 | 94 | 26 | 4 |
| 1921 | 84 | 22 | 7 |
| 1922 | 95 | 18 | 5 |
| 1923 | 116 | 23 | 8 |
| 1924 | 133 | 25 | 6 |
| 1925 | 137 | 33 | 6 |
| 1926 | 199 | 48 | 8 |
| 1927 | 203 | 33 | 5 |
| 1928 | 177 | 32 | 8 |
| 1929 | 51 | 13 | 2 |
| | 1675 | 408 | 86 |

*Cases of latent syphilis occurring in autopsies on adults over twenty-five years of age, in the Pathological Laboratory of the University of Michigan, during the last twenty years.

The distribution of these microscopic lesions of latent syphilis in the various organs and tissues is shown for the first decade in Table II, and for the second decade in Table III. These percentages show the preponderance of the aortic lesions over all others, followed by the meninges, testis and heart.

The microscopical study of the heart and coronary vessels shows the following: In 169 cases of syphilis (1909 to 1919) there were fifty-three cases of coronary sclerosis without thrombosis, nine cases of syphilitic disease of the coronaries, one case of coronary thrombosis

and sclerosis, and no case with a clinical history of angina pectoris. In this decade there were thirteen cases of sudden death without previous anginal history, in the 169 cases of syphilis. Nine of these cases showed marked coronary sclerosis without evidence of syphilitic coronary involvement; four cases showed the lesions of coronary sclerosis and syphilis. In nine of these cases there was a diffuse interstitial myocarditis of the syphilitic type; in four only was there a microscopic picture of myocardial infarction.

TABLE II*

| TISSUE | TOTAL EXAMINED | NO. SYPHILITIC | PER CENT SYPHILITIC | NO. SUSPICIOUS |
|-------------|-------------------|-------------------|------------------------|-------------------|
| Spinal cord | 8 | 4 | 50.0 | |
| Brain | 36 | 19 | 52.78 | |
| Meninges | 40 | 39 | 97.5 | |
| Aorta | 163 | 159 (6 aneurysms) | 97.6 | 4 |
| Heart | 169 | 113 (3 aneurysms) | 66.9 | 5 |
| Liver | 165 | 46 (4 gummas) | 27.8 | 13 |
| Adrenals | 153 | 47 | 30.7 | 1 |
| Pancreas | 163 | 72 | 44.1 | 4 |
| Testis | 137 | 118 | 86.1 | 5 |

*Distribution of Lesions of Latent Syphilis in 169 Cases of Syphilis (142 males, 27 females), in 368 autopsies over 25 years of age, 1909-1919. 43.7 per cent latent syphilitics.

TABLE III*

| TISSUE | TOTAL EXAMINED | NO. SYPHILITIC | PER CENT SYPHILITIC | NO. SUSPICIOUS |
|-------------|-------------------|--------------------|------------------------|-------------------|
| Spinal cord | 60 | 27 | 45.0 | 1 |
| Brain | 198 | 71 (4 gummas) | 35.9 | 2 |
| Meninges | 202 | 168 (2 gummas) | 83.2 | 0 |
| Aorta | 327 | 282 (29 aneurysms) | 86.3 | 7 |
| Heart | 330 | 216 (2 gummas) | 65.5 | 7 |
| Liver | 328 | 102 (12 gummas) | 31.4 | 4 |
| Adrenals | 320 | 145 (1 gumma) | 45.3 | 2 |
| Pancreas | 328 | 98 (2 gummas) | 29.8 | 0 |
| Testis | 264 | 203 | 76.5 | 10 |

*Distribution of Lesions of Latent Syphilis in 332 Cases of Syphilis (275 males, 57 females) in 1289 autopsies over 25 years of age, 1919-1929. 25.7 per cent latent syphilitics.

In this material were two gummas of lung, one of pulmonary artery, two of spleen, two of bone, one of thyroid, two of skin.

TABLE IV

1909 TO 1919. 386 AUTOPSIES IN PATIENTS OVER 25 YEARS OF AGE, WITH 169 CASES OF SYPHILIS SHOWING

| | |
|---|----|
| Coronary sclerosis | |
| Coronary syphilis | 53 |
| Coronary thrombosis and sclerosis | 9 |
| Angina pectoris | 1 |
| Sudden death | 0 |
| Sudden death with coronary sclerosis | 13 |
| Sudden death with coronary syphilis | 9 |
| Sudden death with myocardial infarction | 4 |
| Sudden death with diffuse myocarditis | 4 |
| Myocardial infarction with coronary sclerosis | 9 |
| Myocardial infarction with coronary syphilis | 4 |
| | 0 |

In the decade 1919 to 1929, in the 332 cases of latent syphilis there were 172 cases of coronary sclerosis, and 55 cases showing syphilitic lesions of the coronaries, including one case of gummatous coronary arteritis. In this group there were five cases of coronary occlusion by thrombosis; four of these were associated with coronary sclerosis alone, and one with syphilis of the coronary. There were six cases of angina pectoris in this group; five of these were associated with coronary sclerosis alone, one with syphilis of the coronary main branches. There were twenty-five cases of sudden death in this decade in the syphilitic group; in thirteen of these the coronaries showed arteriosclerosis alone; in twelve cases there were lesions of syphilis in the coronaries, six of these showed both syphilis and sclerosis. Eleven of the cases of sudden death showed myocardial infarction; fourteen showed no infarction, but the picture of a chronic diffuse interstitial myocarditis with fibrosis. Five of the cases of myocardial infarction were associated with occlusion due to coronary sclerosis alone; six were associated with both sclerosis and lesions of syphilis.

TABLE V

1919 TO 1929. 1289 AUTOPSIES IN PATIENTS OVER 25 YEARS OF AGE, WITH 332 CASES OF SYPHILIS SHOWING

| | |
|---|-----|
| Coronary sclerosis | 172 |
| Coronary syphilis (1 gummatous arteritis) | 55 |
| Coronary thrombosis | 5 |
| Coronary thrombosis with coronary sclerosis | 4 |
| Coronary thrombosis with coronary syphilis | 1 |
| Angina pectoris | 6 |
| Sudden death | 25 |
| Sudden death with coronary sclerosis | 13 |
| Sudden death with coronary syphilis | 12 |
| (With both sclerosis and syphilis, 6) | |
| Sudden death with myocardial infarction | 11 |
| Sudden death with diffuse myocarditis | 14 |
| Myocardial infarcts with coronary sclerosis | 5 |
| Myocardial infarcts with coronary syphilis | 0 |
| Myocardial infarcts with sclerosis and syphilis | 6 |

Coronary Syphilis.—Syphilis of the coronaries involves most frequently the smallest intermuscular branches; only rarely are the main divisions the seat of active syphilitic lesions. In the latter the process is usually of the nature of a periarteritis, the small vessels of the adventitia showing perivascular infiltrations and fibrosis, resulting eventually in obliteration. Sclerosis of the intima invariably results, and syphilis must be regarded as one of the causes of coronary sclerosis, as it is of aortic. As aortic syphilis is always associated with coronary syphilis, the mouths of the coronaries may show the most marked sclerosis; in some cases they may be occluded by this process. In severe aortic syphilis this involvement of the coronaries may be limited to the first few millimeters, rarely more than 1 to 2 centimeters, of the main coronary. In our experience this occlusion of the coronary mouths

associated with syphilis is due chiefly to the secondary sclerosis produced by the syphilitic process, and rarely by active syphilitic infiltration or proliferations, which are present about the vasa vasorum in the neighboring aortic wall, and about the small nutrient perivascular branches of the main coronary. In only one of our cases did thrombosis occur in the partially occluded mouth of the coronary. An active proliferating endarteritis due to, or associated with, active syphilis is relatively rare in the larger branches of the coronaries. Gummatous arteritis was found in one very active case of syphilitic aortitis and myoearditis. In one case only was the coronary thrombosis directly associated with an active syphilis of the coronary vessel; in four other cases the thrombosis was due to the secondary coronary sclerosis asso-



Fig. 1.—Active syphilitic perivascular infiltration of small subepicardial coronary vessel.

ciated with the syphilitic process. In all of the cases of acquired syphilis with the exception of two, the syphilitic lesions were chiefly about the descending branch of the left coronary. Involvement of the right coronary and its branches is rare in acquired syphilis, although more common in cases of congenital origin. Myocardial infarction is but extremely rarely the result of a pure syphilitic involvement of the coronary vessels; in the great majority of cases the infarction is caused by occlusion by the atherosclerotic obliteration of the lumen, with or without thrombosis. Syphilis of the smaller branches of the coronaries leads to a slow atrophy and fibrosis of the myocardium, but rarely does it produce an anemic necrosis of the muscle. If cardiac infarction is the essential pathological condition underlying angina pectoris, as it would seem to be in our cases, this failure of syphilis to produce infarc-

tion of the muscle would account for the rarity of an angina pectoris history in our cases of active coronary syphilis without secondary sclerosis.

When we compare the nonsyphilitic cases coming to autopsy during the same two decades, we find that in 1174 nonsyphilitic autopsies there were 412 cases of coronary sclerosis, with six cases of well-defined clinical angina pectoris, eight cases of coronary thrombosis and eight cases of myocardial infarction. In two cases sudden death from coronary thrombosis and myocardial infarction occurred without a history of angina.

TABLE VI*

| PERIOD | NO. AUTOPSIES | CORONARY SCLEROSIS | ANGINA | MYOCARDIAL INFARCTION | CORONARY THROMBOSIS |
|-----------|------------------|-----------------------|--------|--------------------------|------------------------|
| 1909-1919 | 217 | 52 | 1 | 1 | 1 |
| 1919-1929 | 957 | 360 | 5 | 7 | 7 |

*Distribution of Coronary Sclerosis, Angina, Myocardial Infarction and Coronary Thrombosis in the Non-Syphilitic Autopsies in 20-year period, 1909-1929.

In Table VII the percentages of coronary sclerosis, angina, coronary thrombosis and myocardial infarction are compared for the two decades. For 1909 to 1919 the percentage of coronary sclerosis in the nonsyphilitic autopsies was 24 per cent, for the same decade it was 31 + per cent in the syphilitic autopsies. For the decade 1919 to 1929 the percentage of coronary sclerosis in nonsyphilitics was 38 per cent, in the syphilitic autopsies it was 52 per cent. The percentage of angina in the nonsyphilitic autopsies of 1909 to 1919 was 0.46 per cent, in the decade 1919 to 1929 it was 0.53 per cent. In the syphilitic cases there was no case of angina in 1909 to 1919; in 1919 to 1929 the percentage of angina cases was 1.8 per cent. In the decade 1909 to 1919, in the nonsyphilitic autopsies the percentage of cases of myocardial infarction was 0.46, for the decade 1919 to 1929 it was 0.74. In the syphilitic autopsies the percentage of myocardial infarction was 2.4 for the decade 1909 to 1919, and 3.3 for 1919 to 1929.

TABLE VII

PERCENTAGES IN NONSYPHILITICS

| PERIOD | NO. AUTOPSIES | CORONARY SCLEROSIS | ANGINA | MYOCARDIAL INFARCTION | CORONARY THROMBOSIS |
|----------------------------|------------------|-----------------------|--------|--------------------------|------------------------|
| 1909-1919 | 217 | 24% | 0.46% | 0.46% | 0.46% |
| 1919-1929 | 957 | 38% | 0.53% | 0.74% | 0.74% |
| PERCENTAGES IN SYPHILITICS | | | | | |
| 1909-1919 | 169 | 31+% | 0 | 2.4% | 0.58% |
| 1919-1929 | 332 | 52 % | 1.8% | 3.3% | 1.5 % |

The most important thing revealed by the comparison of these charts is the fact that coronary sclerosis, angina pectoris, coronary thrombosis and myocardial infarction have a higher rate of incidence in the syphilitic cases than in the nonsyphilitic. The significance of these

facts must be that syphilis predisposes to the production of coronary atherosclerosis with its attendant pathology. While coronary occlusion, thrombosis, myocardial infarction and angina pectoris are rarely the direct result of active syphilitic lesions of the coronaries, they all occur more frequently in the syphilitic, because of the more marked tendency possessed by the latter to develop severe grades of secondary atherosclerosis of aorta and coronary branches. Syphilis, therefore, secondarily and not primarily, is an important factor in the production of coronary disease and its concomitant angina pectoris.

Still more important is the relationship shown to exist between latent syphilis and sudden cardiac death, as given in Table VIII. Sudden death due to cardiac decompensation and dilatation was almost

TABLE VIII

RELATION OF SUDDEN DEATH TO CORONARY SCLEROSIS AND CORONARY SYPHILIS IN 501 CASES OF SYPHILIS IN YEARS 1909-1929

| | |
|---|----------|
| Sudden death with coronary sclerosis | 22 cases |
| Sudden death with coronary syphilis | 16 cases |
| Sudden death with coronary sclerosis and syphilis | 6 cases |
| Sudden death with diffuse myocarditis | 23 cases |
| Sudden death with myocardial infarction | 15 cases |
| Sudden death with coronary thrombosis | 6 cases |
| Sudden death with coronary thrombosis and sclerosis | 5 cases |
| Sudden death with coronary thrombosis and syphilis | 1 case |

five times as frequent in our latent syphilitics as in the nonsyphilitics. Many of these cases were coroner's autopsies. This bears out the writer's contention as to the importance of cardiac involvement as the frequent cause of death in the syphilitic. Syphilis acts both primarily and secondarily upon the heart. As a secondary factor it plays a large part in the production of aortic and coronary sclerosis; as a primary factor it produces myocardial insufficiency through the slow production of an interstitial fibrosis. Twenty-three of our cases of sudden death showed this lesion alone. In every one of these cases evidence of latent syphilis of the myocardium was found on serial sections, in the form of an increase of stroma cells and localized collections of lymphocytes and plasma cells. Valvular lesions were not present in any one of these cases. We therefore conclude that:

1. Active syphilitic lesions of the larger coronary branches are infrequent. They rarely produce occlusion of the vessel, or lead to thrombosis or myocardial infarction.
2. Arteriosclerosis of the coronaries, coronary occlusion, coronary thrombosis, myocardial infarction and angina pectoris are more frequent in the latent syphilitic than in the nonsyphilitic. Syphilis predisposes secondarily to coronary and aortic sclerosis and their resultant cardiac pathology.

3. Sudden cardiac death was almost five times as frequent in the syphilitic as in the nonsyphilitic autopsies. In the majority of cases this was due to cardiac insufficiency and dilatation, resulting from a diffuse interstitial myocarditis of slight degree, leading eventually to fibrosis.

REFERENCES

- Levine, S. A.: Monograph. Coronary Thrombosis: Its Various Clinical Features, Baltimore, 1930, p. 12, Williams & Wilkins Company.
Stone, W. J.: Angina Pectoris and Coronary Occlusion. With Notes on the Vascular Pathology in Coronary Disease, Warthin Ann. Vol., p. 143, 1927.
Willius, F. A., and Brown, G. E.: Am. J. M. Sc. 168: 165, 1924.

THE PATHOGENESIS OF BROWN INDURATION OF THE LUNG²

ELI MOSCHCOWITZ, M.D.

NEW YORK, N. Y.

IN A PREVIOUS paper¹ I showed that brown induration of the lung results only from those forms of cardiac disorder that are accompanied by a hypertension of the pulmonary circuit. These are, in the order of frequency, mitral disease (especially mitral stenosis), emphysema, pleural adhesions, marked diminution in lung volume from whatever cause, certain cases of marked scoliosis, open ductus Botalli and communications between both sides of the heart. In uncomplicated aortic lesions, in which an increased pressure in the pulmonary circuit does not occur (except perhaps for a short period in the terminal stage of heart failure) I have failed to find brown induration.

Furthermore, such lesions are never found unless arteriosclerosis of the grosser trunks of the pulmonary artery is present. Indeed, arteriosclerosis of the pulmonary vessels is practically never found except when a condition causing hypertension of the pulmonary circulation is present; so that one may say that arteriosclerosis limited to the pulmonary artery is pathognomonic of hypertension of the pulmonary circulation. This relationship is furthermore definitely demonstrable in the utter independence in the incidence of arteriosclerosis of both greater and lesser circulations, and furnishes strong support for the thesis that arteriosclerosis is due to intravascular tension and to no other factor. The detailed reasoning whereby this conclusion was reached has been submitted.²

Associated with arteriosclerosis of the pulmonary arteries lesions of the capillaries are manifest that are pathognomonic of hypertension of the pulmonary circulation. Indeed, these lesions are so characteristic that they enable one by microscopic observation alone to diagnose unerringly gross arteriosclerosis of the pulmonary arteries. The development and senescence of these capillary changes dominate the pathogenesis of the pneumonia of heart disease, and it is for the elucidation of this thesis that this study is submitted.

Normally, the capillaries of the uninjected lung are hardly visible. Here and there one notes a narrow slit, usually containing a single red blood cell. The connective tissue wall of the alveolus is narrow, uniform in thickness, and, with the exception of an occasional bulge of the lining epithelium, the alveolar lining is smooth (Fig. 1).

²Read by title at the American Society of Pathologists and Bacteriologists, New York City, April, 1930.

In the earliest phases of the lesion, the alveolar wall appears beaded. The capillaries are distinctly dilated and the walls are thickened (Fig. 2). In cross-section the capillaries bulge into the alveolar space. In more advanced cases, the dilatation of the capillaries and the thickening of their walls become more pronounced so that the alveolar wall becomes much thicker than normal and the beaded appearance becomes more pronounced (Fig. 3). In this stage, one can already note a profound increase in the connective tissue content of the alveolar wall, this increase consisting almost entirely of the enormously thickened capillary walls. In the latter stage of this lesion, the connective

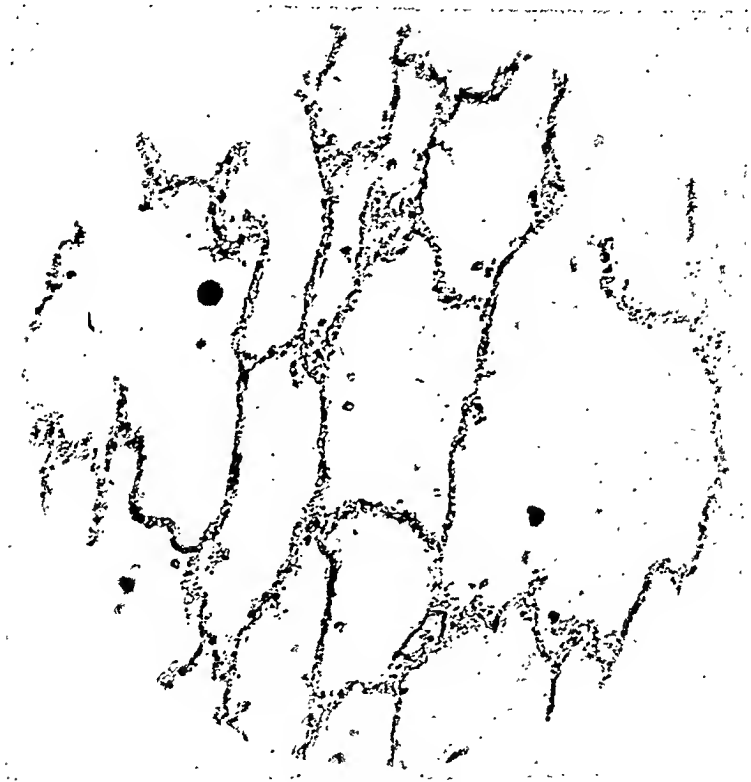


Fig. 1.—Section of normal lung.

tissue content of the alveolar wall becomes comparatively enormous (Fig. 4). The connective tissue is rather cellular, the wall is much thickened, and there is a corresponding narrowing of the alveolar space, accounting in a large measure for the diminution in vital capacity in heart disorders (Peabody³). In some areas hyalinization of the connective tissue is apparent. The capillaries in this stage have become to a great extent obliterated. In the terminal phases, the deposition of connective tissue in the alveolar wall is so great that the alveolar space becomes but a narrow chink, and the lining epithelium, as is the case in all sclerosing organs, reverts to the appearance of the embryonal lung. Capillaries are almost entirely absent, the only vessels persisting in these areas being the greatly sclerosed arterioles

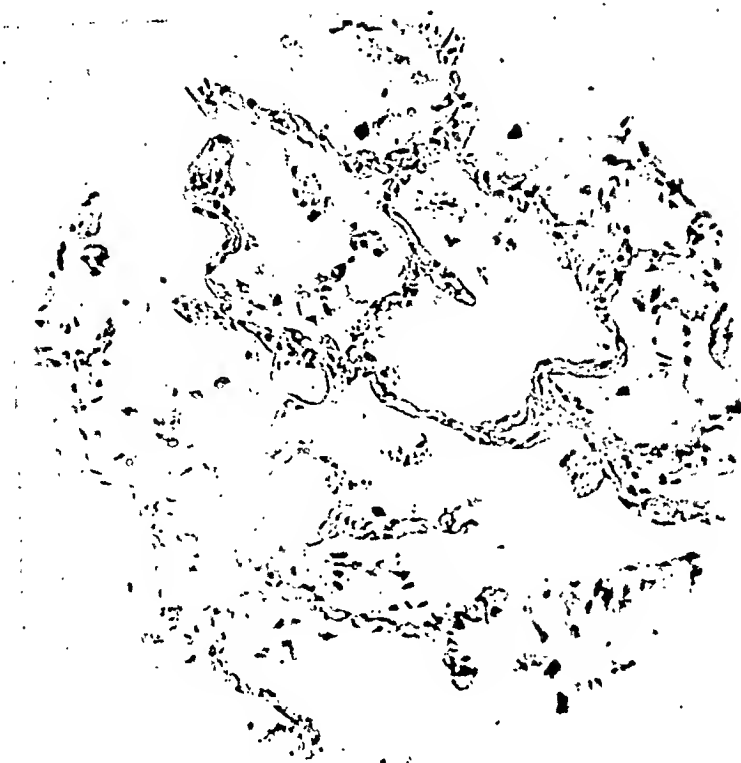


Fig. 2.—Early stage of arteriocalillary fibrosis of the lung consequent to mitral stenosis, showing dilated and thickened capillaries.



Fig. 3.—More advanced stage of arteriocalillary fibrosis of the lung, consequent to mitral stenosis.

and the grosser pulmonary vessels (Figs. 5 and 6). These changes are commonly seen in lungs that have been infarcted, but infarction is not the only cause of the increase in connective tissue. One can see in the immediate vicinity of such areas profoundly sclerotic arterioles with the lumen almost obliterated by intimal thickening. Unquestionably, therefore, diminution in the blood supply is in a large measure responsible for the connective tissue increase.

Grossly, the physical character of the lung corresponds to what we would expect from the microscopic appearance, varying from the suc-



Fig. 4.—Advanced stage of arteriocalillary fibrosis of the lung, consequent to mitral stenosis.

culent, slightly tough organ of the earliest stage to the dense, carneous, fibrous and contracted lung of the terminal stage.

In summary, the capillary lesions of arteriosclerosis and hypertension of the pulmonary circulation represent a true arteriocalillary fibrosis, a term first employed by Gull and Sutton to connote corresponding changes in lesions of the greater circulation associated with hypertension.

In fact, the resemblance between the capillary lesions of the lung in hypertension of the pulmonary circulation and of the capillaries in hypertension of the greater circulation is striking; indeed, in almost every respect the appearances are identical. Both grossly and microscopically, the lesions in the lung represent the same stages as are

witnessed in the kidney in essential hypertension of the greater circulation. Just as in the kidney, where one can place in series organs that reveal only minimal changes in the early stage up to those of profound contraction in the terminal stage, so in the lung one can trace lesions that vary from the slightly carneous lung to that of the



Fig. 5.—Advanced stage of arteriocapillary fibrosis of the lung, consequent to mitral stenosis.

advanced tissue transformation described above. Also, as in the kidney, the sclerosis is associated with, and, in the largest measure, consequent to partial and even complete cutting off of the blood supply by the sclerotic arterioles.

The pathological changes comprised under the term "pulmonary arteriocapillary fibrosis" are uniform, no matter where or how the resistance causing increased tension in the pulmonary circuit is pro-

duced. It is the same, therefore, whether the resistance arises in the mitral ring from a tight stenosis, or within the capillary bed, as in emphysema. Inasmuch as emphysema is in most instances a disease of advanced life, arteriosclerosis is present not only in the lesser but also in the greater circulation, in the latter as the result either of an



Fig. 6.—Final stage of arteriocapillary fibrosis (mitral stenosis) showing extensive fibrosis, sclerosis of the arterioles and reversion of the alveolar epithelium to the embryonal type.

associated hypertension or of decrescent change consequent on prolonged normal intravascular tension. It is, therefore, of considerable interest to report the findings in a case in which the emphysema occurred consequent to a bronchial asthma in an individual thirty-four

years of age, leading to a fatal issue from cardiac failure, a rare phenomenon in a person so young. The case is of especial importance for other reasons; because the arterio-capillary fibrosis was more advanced than any I have ever seen; because it revealed an unusual opportunity to study the lesions of bronchial asthma; and, finally, because the patient was followed clinically from almost the beginning of the disease to its termination.

CASE REPORT

D. H., aged 28 years, when seen by me in 1923 gave a history of having suffered from bronchial asthma for two and a half years. There was no history of asthma or any of the allergic diseases in her family. For four days there had been cough with fever. She had a wheezing dyspnea, and there were sibilant and sonorous râles throughout both lungs; there were dullness and diminished breathing at the right base with a few moist râles. The breathing was diminished also in the right upper lobe. The spleen was palpable. The blood pressure was 140/80 mm. Hemoglobin 95 per cent, red blood cells 4,750,000, leucocytes 6,100, polymorpho-nuclears 80 per cent, lymphocytes 19 per cent, monocytes 1 per cent. The sputum showed a number of Curschmann's spirals and some elastic tissue, but no tubercle bacilli. Culture of the sputum demonstrated anhemolytic and hemolytic streptococci and Micrococci catarrhalis. Blood Wassermann reaction negative. Roentgenograms showed a pneumonia with pleuritic deposits over the right lower lobe and an adherent right diaphragm. The patient recovered from the bronchopneumonia and was discharged at the end of two weeks. Skin sensitization tests showed positive reactions to rye and cheese.

After a remission which lasted a few months the asthmatic attacks recurred, and until her admission to Mount Sinai Hospital on February 1, 1929, she was practically never free. She wandered about Europe and America without relief from any climate or medication. Five or six years ago edema of the ankles began and slowly spread upward involving the entire lower extremities. On admission there was a scarlet flush extending to the mid-thigh of two or three days' duration and attended by soreness and pain. There were also weeping ulcers of ten weeks' duration and tender. For seven months a progressive swelling of the abdomen had been noted. A few years previously there had been progressive diminution of the menstrual flow; three months later there was amenorrhea which persisted. The previous frequent cough with profuse white, tenacious expectoration had become considerably lessened.

Physical Examination.—She was acutely dyspneic and orthopneic. The chest expansion was considerably limited; marked supraclavicular retraction; the pulmonary resonance was increased. The breath sounds were vesicular, the expiration prolonged. There were a few high and low pitched musical râles. The voice and fremitus were unchanged on auscultation. The heart was much enlarged, especially to the right. There was a high pitched, musical murmur at the apex transmitted toward the sternum. At the base of the heart there was a systolic murmur which was short and localized to the second and third spaces to the right of the sternum. A gallop rhythm was at times noted. The rate was irregular, probably due to extrasystoles. The liver was palpable four fingers below the free border of the ribs. The spleen was not felt. Both lower extremities were reddish blue and swollen to twice the normal size by marked pitting edema. Several irregular, shallow ulcers on both legs were covered with a greyish slough. The edema extended up to the buttocks. There was no clubbing of the fingers. The hemoglobin was 102 per cent,

leucocytes 9,600, polymorphonuclears 80 per cent, eosinophiles 4 per cent, lymphocytes 10 per cent, monocytes 4 per cent. The blood urea was 18.0 mg., cholesterol 216 mg., glucose 107 mg. per 100 c.c. The urine varied in quantity between 400 and 600 c.c. a day, and revealed a trace of albumin the first day but none thereafter. The pulse rate varied between 100 and 120; the temperature was normal. Roentgenograms showed "marked enlargement of the heart to the right and to the left, due to advanced mitral lesion." The lungs were much congested. There was a pneumonic process occupying the mesial portion of the right lower lobe. In the right lung there were a number of small shadows which are probably due to emphysematous areas in the lung.

The diagnosis was "asthma, emphysema, hypertension of the pulmonary circulation, myocardial insufficiency." She was treated with digitalis and salyrgan and a Karell diet, but without much improvement. On the fourth day after admission she was found by the nurse deeply cyanotic, gasping for breath and pulseless. She died ten minutes later.

Autopsy Protocol.—Body is that of a well-nourished, adult female, 34 years of age. There is marked cyanosis of the lips, face and fingers. The conjunctivae are markedly congested. The abdomen is distended. Both lower extremities are equally swollen to about twice the normal size, the swelling being most marked below the knees. There is pitting edema over the legs, and on the posterior aspect of the lower half of the legs are noted several irregular, shallow ulcers with a grayish-white base. There are no clubbing of the fingers, jaundice or petechiae. On opening the veins of the neck the blood gushes out as though under pressure, rising to about 3 inches above the level of the vein. It is noted that all the loose alveolar tissue of the body, especially that in the pelvis, shows marked degree of anasarca, the tissues being easily separated from the bony structures.

Chest: The pleural cavities contain a few centimeters of clear fluid. Both lungs weigh 1225 gm. The left upper lobe is bound down to the chest wall by fresh fibrous adhesions, easily torn through. The right lung is bound down more firmly, especially to the diaphragm and to the upper part of the chest wall. These latter adhesions can be broken through only with some difficulty, tearing the parietal pleura off the chest wall. Both lungs are markedly emphysematous, especially the right, which shows on its surface marked bulbous emphysema, the blebs reaching the size of a small plum. The left lung is elastic and crepitant. The cut surface of the upper lobe is dark red, fleshy and hemorrhagic, while the lower lobe reveals a well-aerated and normal appearing surface. The right lung was not opened. The trachea is negative. The bronchi, especially in their smaller branches, show an edematous and inflamed mucosa. There are numerous patches of dense fibrous lung; these patches are most conspicuous in the peripheral portion of both organs.

Heart: The right ventricle and auricle are tremendously dilated and somewhat hypertrophied, taking up the entire anterior aspect of the heart and overlapping the left auricle and ventricle. The left ventricle is normal in size. The heart weighs 525 gm. The myocardium is firm and dark red. The pulmonary orifice measures 8.75 cm. The valves are normal. The aortic orifice is 6.25 cm. in circumference. The wall of the pulmonary artery is thicker than normal, and in the finer branches are noted many small yellow areas of atherosclerosis. The aorta is elastic and, grossly, normal. The coronary arteries are patent. The pericardium is smooth and glistening, and the pericardial sac contains about 200 c.c. unclotted blood. In conjunction with this there is noted a small hemorrhagic spot on the anterior wall of the right ventricle which is apparently due to a puncture wound made by a needle. The tracheobronchial glands are enlarged but are grossly normal.

Abdomen: The peritoneal cavity is filled with about 800 c.c. golden-brown, clear fluid. The peritoneum is smooth and glistening. The intestines are con

gested. The iliac veins are prominent. The liver is smaller than usual, weighing 1425 gm. The capsule is opaque in spots. Cut section reveals the dark-brown mottled appearance of congestion. The portal vein is normal. The gall bladder and biliary tracts are normal. The kidneys are similar in appearance, showing fetal lobulations, and weighing 180 gm. each. The capsules, except where they dip in between the lobulations, strip easily, leaving a smooth dark red surface. Cut section reveals a dark red surface, a widened cortex with normal markings. The bladder is small. The pancreas and adrenals are normal. The spleen weighs 150 gm., is bluish-red and fairly firm. Cut section shows a deep red surface which is not diffuent; the pulp barely scrapes. The Malpighian bodies are rather indistinct.

Genitals: The ovaries are small and equal in size and show no gross disease. The uterus is small and multiparous in type. The venous sinuses in the uterine wall are dilated. The veins in the broad ligament are prominent. The vagina is normal.

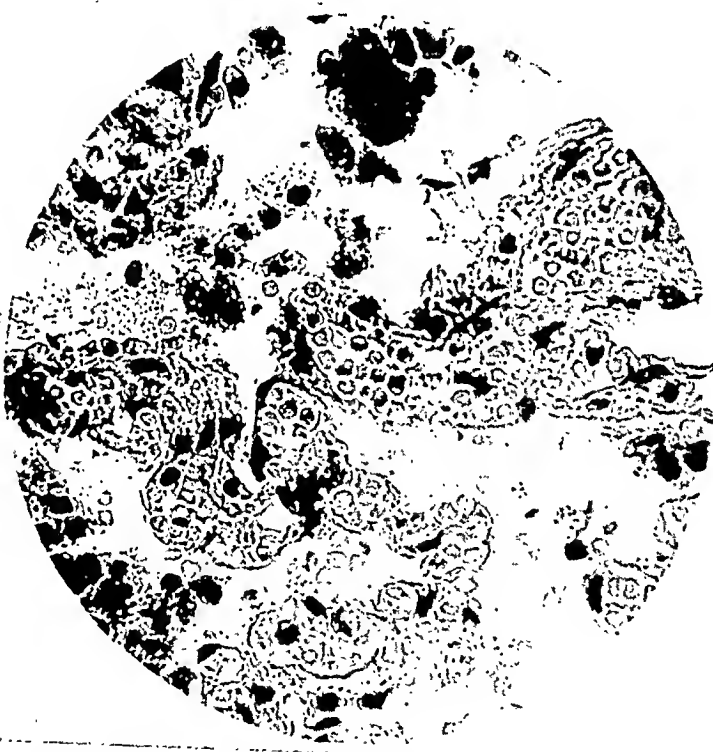


Fig. 7.—Arteriopathy of the lung secondary to asthmatic emphysema, showing extensive dilatation and thickening of the capillaries.

G. I. Tract: The esophagus is bluish-red. The stomach is filled with large amount of semi-fluid, tarry-colored material. The blood vessels are prominent. The entire small intestine shows a congested mucosa, more marked in the proximal portion. The large intestine is filled with a small amount of light yellow feces. The mucous membrane shows no congestion.

Bacteriological Examination: Lung tissue negative for monilia.

Microscopical Examination: The pancreas shows small areas of fibrosis and atrophy of periphery of lobules. The liver shows central congestion and hemorrhages, edema. The thymus shows retrogressive changes. The myocardium is normal. The ovary shows few follicular cysts. The spleen shows the Malpighian bodies prominent; the pulp appears hemorrhagic. The thyroid shows the acini are distended with colloid; the epithelium is flattened. The kidneys are markedly congested. The

lumen of the tubules is filled with cellular debris. Many red blood cells are present in the glomerular spaces.

Lungs: With the low power magnification the section reveals different areas of irregular density varying from a vesicular appearance to that of almost complete consolidation. With the high power magnification the walls of the alveoli in the vesicular areas appear enormously thickened, and the lining intimal endothelium is prominent (Fig. 7). In the consolidated areas the alveoli are very small and in many instances almost completely obliterated. The lining epithelium is high cylindrical and presents the glandular appearance of an embryonal lung. The contraction and obliteration of alveoli is due entirely to an enormous transformation of the alveolar septa into fibrous connective tissue; the capillaries are almost entirely obliterated in these septa (Fig. 8). In tracing the microscopic



Fig. 8.—Advanced stage of arteriocapillary fibrosis of the lung consequent to asthmatic emphysema showing extensive fibrosis of the alveolar walls.

appearance of the septa from the vesicular to the denser consolidated areas one notes the increasing fibrosis, the capillaries becoming fewer in number until they are almost absent. Here and there one notes patches of apparent hyaline change in the walls of the alveoli. The pulmonary vessels are intensely arteriosclerotic: the arterioles, especially in and around the sclerotic portions of the lung, are almost entirely occluded by intimal proliferation, suggesting that part of the sclerosis of the alveolar walls might be the result of shutting off or diminution of the blood supply. The muscular tissue in the septa shows enormous hypertrophy. Most of the alveoli contain the characteristic pigmented "heart failure" cells.

About the bronchi there are extensive areas of fibrosis with lymphatic infiltration. The peribronchial, periarterial and septal lymphatics are filled with many lymphocytes. The bronchial epithelium in places is markedly flattened and in some places consists of a number of layers of squamous cells. The basement membrane is much thickened and has a hyaline appearance. There is hyperplasia of the mucous

glands of the larger bronchi. The bronchial musculature appears hypertrophied. Most of the bronchi contain what appears to be mucinous material. The pleura is thickened by fibrous tissue.

Diagnosis.—Chronic emphysema of both lungs; chronic bronchitis; arteriosclerosis and dilatation of pulmonary artery; dilatation and hypertrophy of the right auricle and ventricle; chronic passive congestion of liver, kidneys, spleen and intestines; ascites; anasarca.

Summary.—A woman acquires bronchial asthma at the age of 26 years. Under observation there is noted a transition from spasmodic asthma to continuous asthma, to emphysema, to the symptom-complex of pure hypertension of the pulmonary circulation, and finally to death from failure of the right side of the heart. At autopsy, dilatation and arteriosclerosis of the pulmonary vessels are found, with hypertrophy of the right ventricle, marked emphysema, patchy fibrosis of the lungs, and the conventional evidences of chronic congestion of the viscera. Microscopically, the lungs reveal profound dilatation of the capillaries and thickening of their walls with transition to obliteration of the capillaries and complete fibrosis of the alveolar septa, lesions, in other words, of an extensive arteriocapillary fibrosis or pneumonia of heart disease.

This is, therefore, an unusually sharp and unmixed case of hypertension of the pulmonary circuit, revealing the independence in incidence between the arteriosclerosis of the lesser circulation and that of the greater circulation, and showing the sequential relationship of arteriosclerosis to pressure changes. In the greater circulation the aorta was normal because the pressure was normal, and the patient did not live long enough for the normal pressure to cause arteriosclerosis (decreseent arteriosclerosis). It has been repeatedly observed that arteriosclerosis of the pulmonary vessels can occur at any age, even during infancy, provided a cardiac disorder is present that gives rise to a heightened circulatory resistance somewhere within the pulmonary circuit, for instance, an open interventricular septum. Decreseent arteriosclerosis is rare in the pulmonary arteries because the intravascular pressure is low, one-sixth that within the aorta, according to Starling.

The case also reveals in striking fashion the genesis of pneumonia of heart disease from a lesion that was primarily not within the heart at all, but from a resistance within the pulmonary capillary bed. Histologically, nevertheless, it differs in no way from the conventional pneumonia of heart disease arising, for instance, from a mitral stenosis.

CONCLUSIONS

1. Brown induration of the lung (Stauungs-induration) only occurs in the forms of circulatory or cardiac disturbance in which a hypertension of the pulmonary circulation can be predicated, no matter where the increased peripheral resistance may be.

2. The lesions are exclusively associated with arteriosclerosis of the pulmonary vessels. Arteriosclerosis of the pulmonary vessels is, there-

fore, pathognomonic of hypertension of the pulmonary circuit and vice versa.

3. The lesion of brown induration of the lung consists essentially in dilatation and thickening of the pulmonary capillaries. It is an "arteriosclerosis" in miniature. Unquestionably, part of the sclerotic process is the result of diminution in blood supply and even infarction of the affected areas.

4. The lesions within the lung parallel exactly those seen in the systemic organs, and especially in the kidney, in hypertension of the greater circulation.

5. A case is reported in which the lesions of the brown induration of the lung were found consequent to a prolonged asthma. Under observation, the patient revealed the transition from a purely functional bronchial asthma to emphysema, to a pure clinical example of hypertension of the pulmonary circulation and finally to death from failure of the right heart.

REFERENCES

1. Moschcowitz: Am. J. M. Sc. 174: 388, 1927.
2. Moschcowitz: Am. J. M. Sc. 178: 244, 1929.
3. Peabody, Meyer, and Dubois: Arch. Int. Med., 17: 980, 1916.

AURICULAR FIBRILLATION AS THE ONLY MANIFESTATION OF HEART DISEASE*

W. M. FOWLER, M.D., AND C. W. BALDRIDGE, M.D.
IOWA CITY, IOWA

IT IS well recognized that auricular fibrillation is ordinarily associated with evident structural change in the heart. This irregularity may, however, be the only manifestation of heart disease, and probably occurs under these circumstances more frequently than is generally appreciated. The present report of ten cases is intended to emphasize this fact.

The following are brief records of our cases:

CASE 1.—D. S., a male medical student, aged 24 years, was admitted to the University Hospital January 8, 1928. He stated that while another student was removing cerumen from his ear with a metal instrument he suddenly felt nauseated and weak, and fainted. He was unconscious about thirty seconds. His fellow students observed a short period of cardiac standstill and then the beginning of the absolute irregularity. When he was examined by one of us thirty minutes later, there was auricular fibrillation, and he complained of palpitation and weakness. The patient walked to the hospital the following morning and the auricles were still fibrillating. Sinus rhythm returned spontaneously after twenty-four hours. On discharge the heart was normal in all respects.

CASE 2.—R. H., aged 27 years, a hospital interne, whose heart had always been perfectly normal, suddenly found himself with auricular fibrillation (checked electrocardiographically) after a swim in an indoor pool. The event occurred in midwinter, at a time when the patient had had no such strenuous exercise for months. The arrhythmia disappeared spontaneously after twenty-four hours. Careful and complete examination at this time showed no evidence of heart disease.

CASE 3.—H. R., male, aged 22 years, was admitted to the University Hospital, March 11, 1930. He complained of paroxysms of rapid heart action which had appeared at irregular intervals for five years. These attacks were induced by excitement, exertion, or alcohol; and in some instances there was no apparent cause. The duration varied from a few minutes to twenty-four hours. The referring physician had observed attacks of auricular fibrillation with a cardiac rate of from 160 to 170 per minute which persisted from six to ten hours. The first examination at the hospital revealed auricular fibrillation. Sinus rhythm was resumed spontaneously, and an attempt to reproduce the auricular fibrillation by exercise resulted in a paroxysm of auricular tachycardia during which the patient experienced an entirely new sensation. Later four ounces of medicinal whisky failed to induce auricular fibrillation. On discharge the heart was entirely normal. Small doses of quinidine sufficed to prevent recurrences.

CASE 4.—V. S., a star football player, aged 20 years, was seen March 7, 1929, because of palpitation of the heart. Following a period of intoxication by bootleg alcohol he was conscious of the sudden onset of a rapid irregular heart action

*From the Department of Medicine University of Iowa.

which persisted for several hours and was associated with a cramp-like sensation in the chest. He had a recurrence of these cardiac manifestations a few days later following another drinking bout. When examined subsequent to the last attack the heart was normal.

CASE 5.—T. R. M., a male, aged 32 years, was admitted to the University Hospital July 30, 1928, because of mild diabetes mellitus. At the age of eighteen years he was in bed for two days with painful joints, but there was no evidence of cardiac involvement at that time. Examination revealed auricular fibrillation which was verified by the electrocardiogram. The patient stated that the irregularity had been present for about three years and was first noticed one morning following a night of extreme intoxication from alcohol of questionable purity. The normal mechanism was restored by the administration of quinidine after which the heart was entirely normal. There was no recurrence of the irregularity. The patient later died following an operation for carcinoma of the rectum, and at necropsy the heart was found to be normal.

CASE 6.—An electrician, aged 25 years, reported to the University Hospital August, 1928, while intoxicated. He complained of a peculiar sensation in the precordium which had been present for about one hour. Upon examination there was a very rapid, irregular heart action with a marked pulse deficit. He denied previous cardiac symptoms, and there was no history of rheumatic or venereal infection. The auricular fibrillation disappeared during the night and did not recur.

CASE 7.—F. S., an Italian male, aged 34 years, was admitted to the University Hospital January 6, 1930. He complained of a queer sensation in the epigastrium which extended over the precordium. He had noticed a rapid heart action with exertion and excitement, but there had been no shortness of breath. The symptoms were first noticed two weeks prior to admission while working in a refrigerator car in which he detected gas. Upon examination auricular fibrillation was obvious and was verified by the electrocardiogram. The normal cardiac mechanism was restored by quinidine after which the heart was normal.

CASE 8.—E. M., male, aged 17 years, was admitted to the University Hospital because of deformities following infantile paralysis. He denied rheumatic fever and venereal infection. When seen prior to an operation on the leg, the heart was normal. Nitrous oxide and ether anesthesia were employed. On the evening after the operation and the following morning auricular fibrillation was noted. Sinus rhythm was resumed spontaneously after twenty-four hours and persisted.

CASE 9.—F. P., a male student, aged 28 years, was examined at the University Hospital April 30, 1929. He was employed in an oil station after school hours. He had always been active, and his past history was unimportant. Two days prior to the examination he noticed a short period of cardiac irregularity while studying. On the morning of the examination the cardiac symptoms recurred on arising, and shortness of breath was experienced. When he was examined in the afternoon, the findings were those of auricular fibrillation. After eleven hours of relative rest the normal rhythm was restored. The heart was then normal. The patient discontinued his work in the oil station, and there has been no further recurrence of the irregularity.

CASE 10.—J. D., male, aged 24 years, was admitted to the University Hospital May 12, 1930. He also was employed in an oil station. About six months prior to admission he noticed the sudden onset of a rapid heart action which lasted for only a few minutes. Three weeks later there was a return of the cardiac disturbance which persisted. When he was examined, the clinical and electrocardiographic manifestations were those of auricular fibrillation. Sinus rhythm was established by the administration of quinidine. Later there was a short paroxysm

of nodal tachycardia, but there has been no further interruption of the normal mechanism. At the time of discharge from the hospital there were no clinical or laboratory evidences of cardiovascular or thyroid disease.

In thirty-five cases collected from the literature, in which auricular fibrillation was the only manifestation of cardiac damage, the irregularity was attributed to a variety of stimuli, including electric shock, intraabdominal diseases, emotion and effort, and to intoxication by many different chemical substances.

In the collected cases and in those of our own series, the factors usually responsible for auricular fibrillation, such as arteriosclerosis, Graves' disease, rheumatic heart disease, and acute infectious diseases, were excluded. It is thus evident that paroxysmal or even permanent auricular fibrillation may be induced in apparently normal hearts. In four of the reported cases the irregularity was permanent. These occurred before the advent of quinidine medication. In a case reported by Reid⁹ normal rhythm was restored by quinidine after two and two-thirds years, and in one observed by Hay and Jones² after five weeks. In one of our patients sinus rhythm was restored by quinidine after two and one-half years of auricular fibrillation. It is to be recalled that this heart (Case 5) was later found to be normal at necropsy. In two other cases in our series auricular fibrillation yielded to quinidine, one after five months and the other after two weeks. The auricular fibrillation in these five cases would probably have persisted also had quinidine not been given.

In four of the thirty-five collected cases the abnormal cardiac mechanism followed electric shocks which varied from 220 to 15,000 volts. This exciting factor is comparable to the faradic current used to produce auricular fibrillation experimentally in animals. The irregularity in those cases lasted from one day to five weeks, and in the latter sinus rhythm was restored by quinidine.

It is interesting to note that intraabdominal disease was held responsible for the auricular fibrillation in eight of the thirty-five cases. Felberbaum and Finesilver⁶ reported a series of five cases, in three of which the cardiac irregularity occurred during or following attacks of gall bladder colic. In one there were four, and in another five paroxysms of auricular fibrillation, and the paroxysms appeared only with attacks of colic. Another patient in this series experienced the cardiac irregularity only during the distress of peptic ulcer. Cowan⁵ recorded two instances of auricular fibrillation, one of which was associated with a gastrointestinal upset following purgation, and the other followed an indiscretion in diet. Wolferth⁷ observed a paroxysm of auricular fibrillation during an attack of acute appendicitis.

The relationship between abdominal symptoms and cardiac irregularities has been recognized for many years. Austin Flint²³ made the following statement in 1885: "Paroxysms of disordered action of the

TABLE I

| CASE | AGE | ETIOLOGY | LONGEST DURATION | RECURRENCE | E.K.G. | REMARKS | REPORTED BY |
|------|-----|--------------------------------|------------------|------------------|-----------|---|--|
| 1 | 35 | Electric shock | 1 day | 0 | Polygraph | Might have been flutter | Laslett ¹ |
| 2 | 35 | Electric shock 250 volts | 5 weeks | 2 attacks | Yes | Remained regular after quinidine | Hay and Jones ² |
| 3 | 31 | Electric shock 220 volts | 1 day | 0 | Yes | | Wartenhorst and Rühl ³ |
| 4 | 37 | Electric shock 15,000 volts | | Repeated | Yes | Better than average endurance before accident | Dick ⁴ |
| 5 | 53 | Exertion and gastric upset | 1 day | 2 attacks | 0 | No evident heart damage | Cowan ⁵ |
| 6 | 58 | Over-eating | Short | Repeated | 0 | Associated with indiscretion in diet | Cowan ⁵ |
| 7 | 65 | Gall bladder colic | 10 hours | 5 attacks | | Only with gall bladder colic | Felberbaum and Finesilver ⁶ |
| 8 | 54 | Gall bladder colic | 10 days | 4 attacks | Yes | Only with gall bladder colic | Felberbaum and Finesilver ⁶ |
| 9 | 34 | Gall bladder colic | 24 hours | 0 | 0 | | Felberbaum and Finesilver ⁶ |
| 10 | 52 | Peptic ulcer distress | 24 hours | Repeated | Yes | Only with gastric distress | Felberbaum and Finesilver ⁶ |
| 11 | 36 | Acute abdominal distress | Short | Repeated | Yes | Extensive postoperative adhesions | Felberbaum and Finesilver ⁶ |
| 12 | | Acute appendicitis | | 0 | 0 | | Wolferth ⁷ |
| 13 | 23 | Cough | Short | Became permanent | Polygraph | Necropsy showed normal heart | Gossage and Braxton Hicks ⁸ |
| 14 | | Sudden exertion | 10 years | Persisted | | Struggled with horse | Hay and Jones ² |
| 15 | 50 | Sudden exertion | Short | 2 attacks | Polygraph | Heart normal the previous day | Hay and Jones ² |
| 16 | 32 | Exertion | 2½ years | 0 | Yes | Stopped with quinidine. Heart normal | Reid ⁹ |
| 17 | 32 | Sudden effort and fright | 14 years | Persisted | 0 | Frightened and climbed over high wall | Hay and Jones ² |
| 18 | 24 | Nervous shock | Short | Repeated | Yes | Very nervous | Semeran ¹⁰ |
| 19 | 22 | Nervous tension. Surgeon | 5 days | 4 attacks | Yes | 1. Paratyphoid. 2 & 4. During long operation. 3. Exertion | Hamburger ¹¹ |
| 20 | 32 | Epinephrine and exertion | 2 hours | 0 | Yes | Very nervous | Smith and Moody ¹² |
| 21 | 39 | Epinephrine and deep breathing | Short | Repeated | Yes | | Smith and Moody ¹² |

TABLE I—Cont'd

| CASE NO. | EXPOSURE | ONSET | REFERENCE | E.C.G. | REMARKS | REPORTED BY |
|----------|----------------------------------|-----------|-----------|-----------|---|---------------------------------------|
| 22 | Alcohol | 36 hours | 0 | 0 | Normal heart | Patterson ¹³ |
| 23 | Alcohol | | 0 | 0 | | Wolferth ⁷ |
| 24 | Alcohol, smoking and over-eating | Few hours | 0 | 0 | Normal heart | Patterson ¹³ |
| 25 | Arsenic 6 gr. | 24 hours | 0 | 0 | Associated gastrointestinal upset | Cassidy. Quoted by Cowan ⁵ |
| 26 | Salvarsan | | 0 | Yes | Gangrene of lung. Chill and collapse after salvarsan | Semerano ¹⁰ |
| 27 | Hydrogen sulphid | Few hours | 0 | Yes | | Robinson ¹¹ |
| 28 | Aspidrin gr. 20 | 3 days | 0 | 0 | Normal heart before | Gupta ¹⁵ |
| 29 | Ether anesthesia | Short | Repeated | Polygraph | Remained normal | Fox ¹⁶ |
| 30 | Digitalis | Short | 0 | Polygraph | Had paroxysmal tachycardia. | Mackenzie ¹⁷ |
| 31 | Diabetic coma | Short | Repeated | | A.P. began with digitalis. Later developed myocardial insufficiency | Borg ¹⁸ |
| 32 | Injury to left chest | 2 days | Persisted | Yes | Normal heart prior to accident | Bullrich and Lacroze ¹⁹ |
| 33 | Kyphoscoliosis | Short | Repeated | 0 | | Bons ²⁰ |
| 34 | | Short | Repeated | 0 | Athletic young male | Levine ²¹ |
| 35 | | 24 hours | 0 | 0 | Athletic young male | Levine ²¹ |
| 36 | Instrumentation of ear | | | | Syncopeal attack followed by fibrillation | This report |
| 37 | Exertion | 24 hours | 0 | Yes | Disappeared spontaneously | This report |
| 38 | Exertion, excitement, alcohol | 10 hours | Repeated | Yes | Also nodal paroxysmal tachycardia | This report |
| 39 | Alcohol | Short | Repeated | 0 | Two attacks after drinking | This report |
| 40 | Alcohol | 2½ years | 0 | Yes | Stopped with quinidine. Heart normal at necropsy | This report |
| 41 | Alcohol | Short | 0 | 0 | | This report |
| 42 | Gas in refrigerator car | 2 weeks | 0 | Yes | Stopped after quinidine | This report |
| 43 | Anesthesia | Short | 0 | 0 | Heart normal before and after attack | This report |
| 44 | Oil station | 11 hours | 2 attacks | 0 | No recurrence since change in occupation | This report |
| 45 | Oil station | 2 months | Repeated | Yes | No recurrence since change in occupation | This report |

heart are often accompanied by gastric flatulence, and gaseous eructations afford relief." Hoover²⁴ has contributed the most comprehensive discussion of the subject in the last edition of Osler's *Modern Medicine* (1927). He cites a case in which functional heart-block resulted from gaseous distention of a stomach diffusely involved by carcinoma: "Such symptoms must certainly have been caused by excitation near the cardia and not from upward displacement of the diaphragm." In a second case, premature beats were induced whenever there was as much as a pint of water in the stomach. This he attributed to a low threshold for the vagus reflex. Finally he reported the following case: "A man who for years has suffered from stomach symptoms (that have never been satisfactorily explained) on several occasions developed auricular fibrillation. During the attacks neither ventricle was enlarged but the right auricle was enlarged to the right of the sternum. These attacks accompanied functional disturbances in the stomach motility and ceased without medication just as suddenly as they began. Thus far the heart has shown no evidences of disease and although for several years these attacks of auricular fibrillation have recurred at irregular intervals, the heart has apparently lost none of its reserve energy."

The mode of production of auricular fibrillation in disease of the abdominal viscera is of special interest. In all of the reported cases the offending lesion was in a viscus supplied by the vagus nerve. It would seem that a reflex stimulation of the heart through the vagus was probably the exciting factor. This feature is best illustrated by the first case in our series in which stimulation of the sensory endings of the vagus in the external auditory canal produced cardiac syncope which was followed by auricular fibrillation. Other factors such as pain, fright, exertion, infection and intoxication were not present.

Excitement, exertion and high nervous tension appeared to be factors in cases reported by Hay and Jones,² Smith and Moody,¹² Semerau,¹⁰ Hamburger,¹¹ and by Reid.⁹ Hay and Jones reported a case of auricular fibrillation in a patient who was frightened by a dog and climbed over a high wall, and another in a man who struggled with a horse. In both instances the irregularity persisted. A nervous element seemed to be the outstanding feature in the patients studied by Smith and Moody. In one, excitement regularly induced a rapid irregular heart action, and attacks were also precipitated by the administration of epinephrine and by deep breathing. The second case was very similar. In the patient studied by Semerau the disordered cardiac mechanism was induced by the nervous shock of an explosion. Hamburger's patient, who was a surgeon, experienced his first paroxysm of auricular fibrillation during the course of paratyphoid fever. His second and fourth attacks occurred during long operations which were attended by high nervous tension, and the third attack

was attributed to exertion. In one of our cases auricular fibrillation followed swimming which was unassociated with emotion.

The importance of impure alcohol in the production of auricular fibrillation deserves special mention. In four of our patients and in three of the collected cases the onset of the irregularity followed a drinking bout. In our cases the alcohol was of questionable purity, and the others occurred in the United States since the advent of the Eighteenth Amendment. One of our patients who stated he always experienced rapid irregular heart action after drinking alcohol was not affected by four ounces of medicinal whisky. It would seem that the irregularity might be attributed to some impurity in the alcohol.

In three of our cases there was a possibility of carbon monoxide inhalation. Conduction defects have been reported by Colvin²⁵ and by Haggard²⁶ in very severe grades of carbon monoxide poisoning. None of our patients inhaled enough of the gas to produce symptoms and certainly not enough to produce the anoxemia which is assumed to be the cause of the conduction defects. The gas which the patient in Case 7 encountered in the refrigerator car was no doubt from the charcoal burner with which such cars are heated during the winter. The possibility of carbon monoxide poisoning under such circumstances is well recognized by railroad authorities. The other two patients were attendants at gasoline stations, one of whom was exposed to fumes in a closed garage. These patients were very careful in the handling of ethyl gasoline but both inhaled some volitalized gasoline of all grades.

In ten of the collected cases and one of our own, auricular fibrillation was attributed to such agents as arsenic, salvarsan, hydrogen sulphide, aspirin, ether anesthesia, digitalis, diabetic coma, injury to the chest, spinal deformity and cough. In the case in which arsenic was mentioned as the probable precipitating factor there was an associated gastrointestinal disturbance which may have been important in the production of the auricular fibrillation. There is also a possibility of vagal stimulation in the case in which the irregularity was precipitated by coughing. Finally, Levine²¹ recorded two healthy young adults with paroxysmal auricular fibrillation for which he gave no etiological factor.

The various exciting causes appear to be unrelated. The induction of the auricular fibrillation under these circumstances is possibly dependent upon some common basic disturbance in the auricles. It is not possible to exclude minor degrees of cardiac damage as being fundamentally responsible for the altered rhythm. If we grant an anatomical basis, the damage is no doubt of minor importance compared to that ordinarily encountered and probably is confined for the most part to the auricles. It may be a temporary lesion or a disturbance of function alone. In some instances the lesion may subsequently pro-

gress to the point where structural changes can be detected by the present methods of examination. The future course of these patients may decide this question.

SUMMARY

Ten patients are reported in whom auricular fibrillation was the only evidence of cardiac disease. The factors usually responsible for this irregularity were excluded. The age ranged from seventeen to thirty-four years, and all except two were under thirty years of age.

In seven cases the auricular fibrillation was paroxysmal, while in three it had persisted for periods of two weeks, five months, and two and one-half years respectively. In each of the latter instances sinus rhythm was restored by quinidine. The auricular fibrillation in these three cases would probably have continued had quinidine not been given. The patient who had auricular fibrillation for two and one-half years later came to necropsy, and the heart was regarded as grossly and microscopically normal.

In one of our cases the auricular fibrillation was attributed to the removal of cerumen from the external auditory canal, one to exertion, four to alcohol, one to carbon monoxide, one to ether and nitrous oxide anesthesia and two were in attendance at gasoline stations.

In the thirty-five cases collected from the literature the auricular fibrillation was attributed to such stimuli as electric shock, diseases within the abdomen, emotion and effort and intoxication by various chemical substances.

Abdominal disease and alcohol were the most common exciting agents. In the former group it is believed that a reflex stimulation over the vagus contributed to the production of auricular fibrillation.

REFERENCES

1. Laslett, E. E.: A Paroxysm of Auricular Fibrillation Caused by Electric Shock, *Brit. Med. J.*, 1: 919, 1927.
2. Hay, John, and Jones, H. W.: Trauma as a Cause of Auricular Fibrillation, *Brit. Med. J.*, 1: 559, 1927.
3. Jaksech-Wartenhorst, R., and Rühl, J.: Vorhofflimmern nach elektrischem Trauma, *Ztschr. f. d. ges. Exp. Med.*, 50: 110, 1926.
4. Dick, Anna: Ueber das Vorkommen von chronisch sich wiederholenden Anfällen von Vorhofflimmern nach Starkstromunfall, *Schweiz. med. Wchnschr.*, 9: 1176, 1928.
5. Cowan, J.: Causes of Auricular Fibrillation, *Quart. J. Med.*, 22: 237, 1929.
6. Felberbaum, D., and Finesilver, B.: Transient Auricular Fibrillation in Abdominal Diseases, *AM. HEART J.*, 2: 416, 1927.
7. Wolferth, C. C.: Intermittent Auricular Fibrillation, *Arch. Int. Med.*, 36: 735, 1925.
8. Gossage, A. M., and Braxton Hicks, J. A.: On Auricular Fibrillation, *Quart. J. Med.*, 6: 435, 1912-13.
9. Reid, W. D.: Auricular Fibrillation in an Apparently Normal Heart, *Bost. M. & S. J.*, 197: 1213, 1927.
10. Semerau, M.: Ueber Rückbildung der Arrhythmia perpetua, *Deut. Arch. f. klin. Med.*, 126: 161, 1918.

11. Hamburger, W. W.: The Recognition and Treatment of Different Types of Auricular Fibrillation, *Med. Clin. N. A.*, 5: 1705, 1922.
12. Smith, F. M., and Moody, W. B.: The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, *Arch. Int. Med.*, 32: 192, 1923.
13. Patterson, R. V.: Transient and Recurrent Auricular Fibrillation, *J. A. M. A.*, 82: 453, 1924.
14. Robinson, G. C.: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphid Poisoning, *J. A. M. A.*, 66: 1611, 1916.
15. Dutt Gupta, A. K.: A Case of Auricular Fibrillation After Aspirin, *Indian Med. Gaz.*, 63: 531, 1928.
16. Fox, G. H.: The Clinical Significance of Transitory Delirium Cordis, *Am. J. M. Sc.*, 140: 815, 1910.
17. Mackenzie, James: *Digitalis, Heart*, 2: 273, 1910-11.
18. Borg, J. F.: Diabetic Acidosis; Etiological Factor in Production of Auricular Fibrillation, *Minn. Med.*, 11: 580, 1928.
19. Bullrich, R. A., and Lacroze, A.: Post-traumatic Heart Block, *Revista de la Soc. de Med. Interna, Buenos Aires*, 6: 241, 1925. (Abstract *J. A. M. A.*, 85: 1519, 1925.)
20. Boas, E. P.: The Cardiovascular Complications of Kyphoscoliosis With Report of a Case of Paroxysmal Auricular Fibrillation in a Patient With Severe Scoliosis, *Am. J. M. Sc.*, 166: 89, 1923.
21. Levine, S. A.: Auricular Fibrillation: Some Clinical Considerations, *Am. J. Med. Sc.*, 154: 43, 1917.
22. Korns, H. M.: Personal Communication.
23. Flint, Austin: *Pepper, System of Medicine, Functional Disorders of the Heart's Action*, 1885, vol. 3, p. 749, Lea Brothers & Co.
24. Hoover, C. F.: *McCrac, Osler's Modern Medicine, Functional Disease of the Heart*, Philadelphia, 1927, vol. 4, p. 600, Lea and Febiger.
25. Colvin, L. T.: Electrocardiographic Changes in a Case of Severe Carbon Monoxide Poisoning, *AM. HEART J.*, 3: 484, 1928.
26. Haggard, H. W.: Studies in Carbon Monoxide Asphyxia, I, The Behavior of the Heart, *Am. J. Physiol.*, 56: 390, 1921.

THE CHANGES IN CIRCULATION FOLLOWING BIRTH*

BRADLEY M. PATTEN, PH.D.

CLEVELAND, OHIO

THE results of several recent investigations indicate that certain long cherished traditions as to the fetal circulation must be relinquished. That this new information has come fragmentarily from various independent workers and is still mutually confirmatory gives it especial weight. Since interpretation of the changes in circulation which follow birth must start from fetal conditions as a basis, it seems pertinent to reexamine both these closely related subjects in the light of our present information.

Controversies concerning the course of blood through the fetal heart have been smouldering, with periodic outbreaks, ever since the times of Harvey. The historical phases of the subject have been thoroughly covered by Pohlman⁹ (1909) and more recently by Kellogg³ (1928). The striking thing is the persistence of the Sabatier¹¹ (1791) doctrine that the entire inferior caval stream carrying the freshly returned placental blood passes directly through the foramen ovale to the left atrium, while the superior caval current of blood, depleted by a systemic circuit, passes with little or no mingling into the right ventricle. Possibly there exists, because of greater familiarity with the adult circulation where separation of pulmonary from systemic blood is so strikingly maintained, an unconscious bias toward interpreting the fetal circulation in terms of blood currents which maintain their identity. Whatever the underlying reasons may be, current textbook illustrations bear eloquent testimony as to the tenacity of the Sabatier conception in the face of an increasing accumulation of evidence against it.

Early injection experiments (e.g., Reid,¹⁰ 1835) appeared to give some support to the Sabatier theory. But these experiments made with heavy starch masses in dead material, when reviewed in the original, appear too equivocal to justify the wide citation they have received.

Pohlman⁹ (1909) carried out the first really critical experiments devised to ascertain the course of blood through the fetal mammalian heart. In living pig embryos he injected colored starch grains into the circulation and, by repeated counts of the grains appearing in blood recovered from the right and left heart, demonstrated that mixing of inferior and superior caval blood occurred in the right atrium. Clear cut as were Pohlman's results, they had little apparent influence on the propagation of the Sabatier theory of crossed pure currents.

*From the Laboratory of Histology and Embryology, Western Reserve University, School of Medicine.

In 1928 Kellogg³ repeated and extended Pohlman's experiments. Working with cats and dogs as well as pigs, and varying both the sites of injection and of recovery, Kellogg amply confirmed Pohlman's conclusions. Moreover, in a later paper (1929) Kellogg⁴ has reported oxygen determinations made on blood recovered from both cavae and from both sides of the fetal heart which clearly indicate that the left atrium does not receive, by way of the foramen ovale, unmixed inferior caval blood freshly returned from the placenta.

Indication that the results of these experiments on animals are applicable to the human fetus is given by the work of Patten, Sommerfield, and Paff⁷ (1929) on the functional capacity of the foramen ovale. Their study of the interatrial opening in the human fetal heart showed

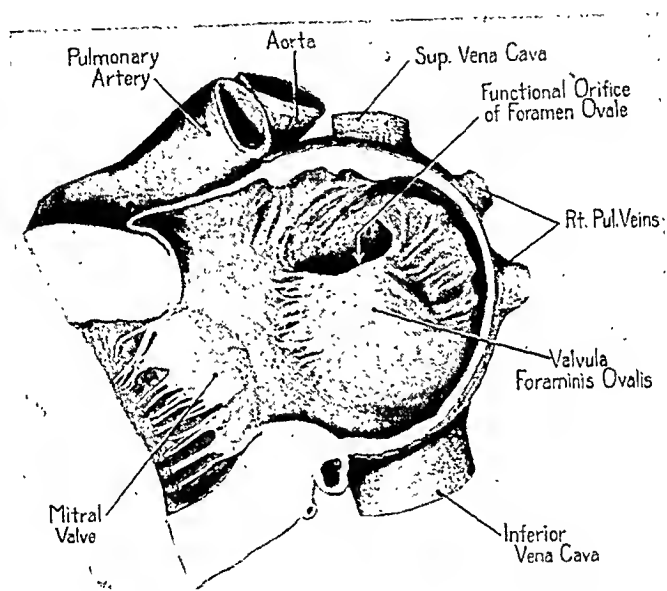


Fig. 1.—Interior of the left atrium of the human heart at birth ($\times 1\frac{1}{2}$); based on a photograph of a scale model retouched from direct study of a group of normal specimens. The valvula foraminis ovalis is shown in the position assumed when a stream of fluid is forced through the inferior vena cava.

that the apparent capacity of the septal orifice is greatly reduced by the manner in which the valvula foraminis ovalis is attached to the septum. The measurements showed an effective interatrial communication less than 43 per cent of the cross-sectional area of the inferior caval inlet (Figs. 1 and 2). Even making the forced assumption of a rate of caval inflow sufficiently strong to form a definite current directed at the foramen ovale, this current could not pass through a crooked passage less than half the size of the caval inlet. Eddying back of more than half the inferior caval stream would inevitably result in the same sort of mixing of placental and systemic blood in the right atrium of the human fetus that Pohlman and Kellogg have demonstrated experimentally in other mammals.

The restricted functional orifice of the foramen ovale is of significance for other conditions than the mixing of blood currents in the right atrium. By reason of its small size the foramen ovale alone cannot pass on to the left side of the heart nearly enough blood to equalize intake on the left with intake on the right. In view of the fairly equal development of the two sides of the fetal heart any assumption that they do not handle approximately equal amounts of blood is untenable. The obviously neglected factor in this situation is the pulmonary circulation.

It is commonly stated that before birth there is very little blood passing through the pulmonary circuit. There seems to be no evidence of any sort adduced in support of this dictum. As far as one can trace its origin it is entirely the outgrowth of a theory as to the mechanism by which a radical rerouting of blood through the fetal heart is supposed to be brought about at the instant of birth. It has the unmistakable odor of teleology to postulate a capacious but virtually unused vascular plexus developing in the growing lungs, ready at the instant of birth to receive a suddenly rerouted current of blood carried to the lungs for oxygenation. While there are not as yet available any quantitative determinations of the blood flow through the fetal lungs, all the implications are against the current view that the pulmonary circulation is negligible. It is out of line with everything known about the development of the vascular system to think of vessels growing beyond a capacity consonant with their present activities. Nor is this argument by analogy the only angle of approach open. Injection or perfusion of the vascular tree of uninflated lungs seems to offer little if any more resistance than injection of inflated lungs. Moreover, measurements of the pulmonary vessels in individuals just before birth show them to be of virtually the same capacity as they appear in other individuals that died after breathing for two or three days.* The actual size of the fetal pulmonary veins as determined by these measurements indicates that they bring into the left atrium a volume of blood somewhat greater than that contributed by way of the restricted functional orifice of the foramen ovale. The fact that the left side of the heart receives much less blood by way of the foramen ovale than hitherto believed, but receives a correspondingly greater amount from the pulmonary circuit, leaves undisturbed our conception of an approximate right-left balance of cardiac load during fetal life. It does, however, radically lessen if indeed it does not eliminate entirely, the abrupt increase in pulmonary circulation which it was necessary, on the old basis, to postulate at the moment of birth.

*These figures for the pulmonary vessels and those that follow for other cardiac orifices are given from preliminary tabulations of work still in progress (Patten and Toulmin⁸). None of the average measurements here given are based on fewer than forty hearts. In some instances more than 100 cases have already been measured. The close agreement of sample group averages indicates that the results of the greater number of individual measurements it is planned to make before publication of the detailed data will differ but fractionally from those given here.

Most significant from the standpoint of postnatal changes are the additional facts that the pulmonary arteries are about the size of the umbilical arteries and the total cross-sectional area of the pulmonary veins about the same as that of the umbilical vein. The placental circuit adequately takes care not only of oxygenation, but also of food intake and waste elimination. If, therefore, the pulmonary vessels are carrying a circulation in any way consonant with their size there is enough blood already going to the lungs before birth to care for oxygenation as soon as the lungs are ventilated.

Fig. 2 summarizes graphically the points discussed above and indicates the revisions in the current interpretation of the fetal circulation

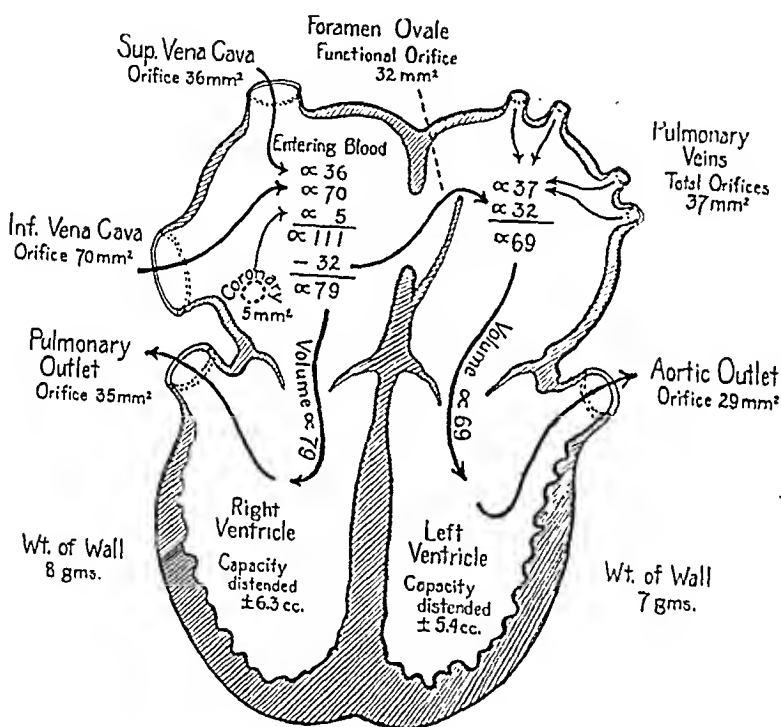


Fig. 2.—Schematic diagram showing dimensions of 20 gram heart from normal full-term fetus. For the sake of simplicity the measurements for this typical heart are given to the nearest integer. Tabulated measurements from a series of over fifty hearts ranging from 15 to 30 grams show the constancy of the significant relationships here indicated. (Patten and Toulmin.)

that they entail. There is mixing of the blood in the right atrium instead of crossed "pure currents." The restricted functional orifice of the foramen ovale brings, instead of practically all, less than half the blood entering the left atrium. On the basis of vessel size, the fetal pulmonary circuit brings in more than half the blood entering the left atrium. The blood shunted from right to left through the foramen ovale does not quite raise the blood volume estimated as entering the left atrium to equality with that entering the right. That this is a real difference and that the load carried by the right and left sides of the heart is not absolutely balanced is confirmed by the slightly

greater size of the right ventricular lumen, the slightly greater weight of the right ventricular musculature and the somewhat greater size of the pulmonary than the aortic outlet. These facts all accord with the characteristic right ventricular preponderance exhibited by electrocardiograms of the neonatal heart.

It is unwise to draw too specific conclusions about the circulation from such measurements alone. At present, however, there are available practically no pressure or volume determinations on the fetal circulation. In the sizes of the channels we have at least the start of a quantitative basis of interpretation hitherto lacking. That these measurements are not without functional significance is indicated by some simple comparisons.

In the fetus, aortic and pulmonary pressures may be assumed to be equal because of the free communication of these vessels through the ductus arteriosus. This assumption is in accord with the only experimental evidence we have on blood pressures in the fetal heart, Pohlman's observations that blood rises to equal heights in capillary tubes inserted in the right and in the left ventricles. If the pressures are equal, the relative size of the arterial outlets and the relative weights of the ventricular walls should both be indicative of the amount of blood handled by the right and left sides of the heart. In that case we should expect the two ratios to equal each other. That is:

$$\frac{\text{Right Ventricular Weight}}{\text{Left Ventricular Weight}} \text{ should equal } \frac{\text{Area Pulmonary Outlet}}{\text{Area Aortic Outlet}}$$

Writing into this proportion the actual measurements made on fetal hearts:

$$\frac{8}{7} \text{ should equal } \frac{35}{29}$$

The correlation figures at 0.94 + where 1 is the expectation.

Since the atria of the fetal heart are in open communication, some of the greater intake of the right atrium will tend to be passed on by way of the foramen ovale to the left atrium. If the blood entering the atria is proportional to the size of their vascular inlets, as is probable with the very low pressure there existing, we can indicate conditions empirically thus:

| <i>Entering Right Atrium</i> | | | <i>Entering Left Atrium</i> | | |
|-------------------------------|--------------------------|---|---|-------------------------|--|
| Orifice of superior vena cava | 36 sq. mm. | | | | |
| Orifice of inferior vena cava | 70 sq. mm. | | | | |
| Orifice of coronary sinus | 5 sq. mm. | | | | |
| | <hr/> | | | | |
| Total | 111 | | Total cross-sectional area of pulmonary veins | 37 sq. mm. | |
| | <hr/> | | | | |
| | -32 | → | Functional Orifice Foramen Ovale | 32 sq. mm. | |
| | <hr/> | | | | |
| Blood volume | ∝ 79 sq. mm. inlets | | | ∝ 69 sq. mm. inlets | |
| | ↓ | | | ↓ | |
| | Entering right ventricle | | | Entering left ventricle | |

If these figures are functionally significant, the ratio of blood received by the two ventricles should equal both the ratio of right to left ventricular weight and the ratio of pulmonary to aortic outlet. Substituting the figures obtained from actual heart measurements:

$$\frac{79}{69} \text{ should equal } \frac{8}{7} : \text{Correlation computes at } 0.98$$

And:

$$\frac{79}{69} \text{ should equal } \frac{35}{29} . \text{Correlation computes at } 0.94$$

These methods of comparison are, of course, crude from the mathematical standpoint and quantitatively the results should be regarded as tentative. When pressure measurements and flow determination can be added to the available evidence, more critical mathematical methods must be applied to the problem. Pending this time the existence of a roughly 8-to-7 relation between (1) right and left ventricular intakes as estimated empirically from the measurements of vascular orifices, (2) right and left ventricular weights, (3) right and left ventricular capacities and (4) pulmonary and aortic outlets, may be regarded as indicative of the nature of the right-left functional balance in the fetal heart.

Because the Sabatier idea of crossed blood currents in the right atrium has been so long entrenched, the conception that there is mixing of the blood in the right atrium is likely to meet with more resistance than either the idea of a prenatal pulmonary circuit of considerable volume, or the conception of the right-sided preponderance of the fetal heart. Such mixing of the blood may seem inefficient compared with condition in the adult, but this is a one-sided comparison. The fetus is an organism in transition. Starting with a simple ancestral plan of structure and living an aquatic life, it attains its full heritage but slowly. It must be viewed as much in the light of the primitive conditions from which it is emerging as in comparison with the definitive conditions toward which it is progressing. Below the bird-mammal level, circulatory mechanisms with partially divided and undivided hearts and correspondingly unseparated blood streams meet all the needs of metabolism and growth. Maintenance of food, oxygen, and waste products at an average level which successfully supports life does not depend on "pure currents," although such separated currents undoubtedly make for higher efficiency in the rate of interchange of materials. From a comparative viewpoint, the fact that the mammalian fetus is supported by a mixed systemic circulation seems but natural. Moreover, if the fundamental competence of such a circulation is emphasized rather than the respects in which it falls short of the perfected adult mechanism, we are not forced to postulate a series of abrupt and profound changes in the circulation at the time of birth,

nor are we continually puzzled by the "seemingly impossible size" of septal defects such as are not infrequently carried without serious handicap into maturity and even old age.

The changes occurring in the circulation postnatally must be re-evaluated in the light of this altered conception of the fetal circulation. According to the conventional interpretation, tying the cord reduces the volume of blood flowing from the inferior vena cava into the right atrium and thence through the foramen ovale to the left atrium. With the first breath, the preformed, but hitherto practically unused, pulmonary vessels suddenly open and allow a rush of blood to pass into the lungs. By the very power of its surge into the left atrium the blood returning from the lungs forces the valvula foraminis ovalis to close against the weakened caval current impinging on its right atrial face. Within a day or two, or perhaps a week, the valvula fuses to the septum and seals the foramen ovale. Inflation of the lungs shifts visceral relations, putting the ductus arteriosus on so much of a stretch that blood can no longer pass freely through it and, presto! the newborn infant has an adult type of circulation. It is a dramatic story lending itself well to diagrammatic exposition within brief compass, but it will not stand scrutiny.

In its older form, the idea of the immediate closure of the foramen ovale was crudely mechanical. There was supposed to be an active shutting off of this passage which forced a rerouting of the blood through the heart. If such closure failed to occur, cyanosis and death were supposed to result. One will find this view still expressed in many current textbooks of embryology and obstetrics. And case after case can be found in present-day hospital and public health records implying the same viewpoint by accusing an open foramen ovale of being the cause of death in a neonatal individual where an open foramen ovale is absolutely normal. Belated recognition of the long-known fact that closure of the foramen ovale is not completed until several months after birth is slowly forcing a retreat from such traditions. The present view is essentially that although anatomical closure of the foramen ovale is delayed, its functional closure is immediate.

Even this modified conception of an immediate closure which is functional rather than anatomical is a corollary of the old Sabatier hypothesis. The first critical event leading toward closure is supposed to be a reduced inferior caval current due to interruption of the placental circuit. If, as recent work clearly indicates, there exists no pure current of inferior caval blood traversing the right atrium and making its way directly through the foramen ovale, this contention loses all weight. If there is free mingling of the blood currents entering the right atrium, flow through the foramen ovale must be determined by the difference between the rate of intake and the resultant pressures which exist on either side of the interatrial septum. Unfor-

Unfortunately we have no experimental data on these critical matters. But what effective reduction can interruption of the placental circuit bring about in the relative volume or pressure of blood entering the right atrium as compared with that entering the left? No maternal blood was coming to the fetus from the placenta. After the tying of the cord, as before, all the blood in the systemic circuit must return to the right atrium. Possibly after the placenta is cut off, relatively more blood enters through the superior cava. But change in the relative amount of blood returned by the two cavae will not alter the pressure relation between right and left atria. As far as the heart is concerned the immediate result of tying off the umbilical vessels is merely to eliminate from the fetal circulation the blood that happened to be passing through the placenta at the moment. It can have no more effect on relative pressures in the two atria than loss of the same amount of blood by superficial hemorrhage. One might as well try to effect the closure of the *valvula foraminis ovalis* by carrying out simultaneously hyperdermoeclysis in the drainage area of the superior cava and venesection in the territory drained by the inferior cava.

As to the ductus arteriosus being abruptly occluded by traction on it incident to the first inspiration, a little dissection and some experimental pulling and hauling on that tough-walled vessel will make one exceedingly skeptical. Furthermore in case after case of congenital aortic stenosis the ductus arteriosus remains open, pouring a supplementary stream into the deficient aortic current. Conversely in cases of true congenital pulmonary stenosis the ductus quite commonly remains open with blood from the aorta going through it to the lungs in reverse of the normal direction of fetal flow. If in such experiments, obligingly performed for us by nature, complete inflation of the lungs fails, over a period of months or even years, to effect the closure of a ductus arteriosus which is carrying merely a supplementary blood current from a more or less crippled heart, how can we look to such a mechanism to close off abruptly at the moment of birth, a blood stream equal in power and volume to that of the isthmus part of the fetal aortic arch? (Fig. 3.)

The idea that the pulmonary flow is negligible before birth and rises abruptly to full power with the beginning of respiration is, as far as a diligent search of the literature reveals, pure dogma. As was stated above, no direct observations have been made on the volume of the pulmonary flow before birth, but the circumstantial evidence, first of the size of the vessels and second of the right-left unbalance that would exist in the fetal circulation if these vessels were not operating at capacity, strongly indicates that the pulmonary circuit before birth is a dynamic factor which cannot be ignored. But, although the pulmonary vessels are equivalent in size to the umbilical vessels, the total

cross-sectional area of the pulmonary veins at the time of birth is approximately only one-third of the total cross-sectional area of the veins entering the right atrium. (Fig. 2.) It entails an incredible series of assumptions to juggle pressures and rate of flow in such a manner as instantaneously to balance the output of one group of veins against the output of another group having three times their bore. Yet this is demanded by the theory that an immediate closure of the *valvula foraminis ovalis* is brought about by prompt equalization of left and right atrial pressures.

The existence of doubt concerning, or positive evidence against, each separate event in the chain of happenings invoked to throw the switches for an immediate and radical rerouting of blood at the time of birth should give us pause. Is not the very existence of such abrupt changes as unsupported as the elaborate series of occurrences supposed to explain them? Let us look without preconceived prejudice

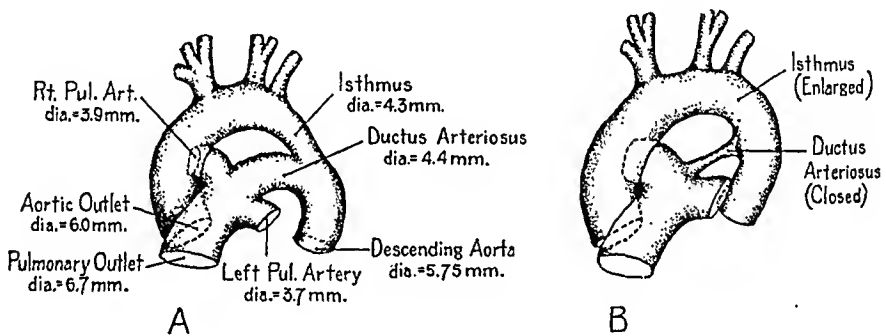


Fig. 3.—Diagrams showing the characteristic postnatal change in the isthmus region of the aortic arch. A. Fetal condition at full term. The vessel diameters are averages from the measurements of thirty cases. B. Typical configuration three to four months after birth. Note the enlargement of the isthmus portion of the aortic arch which accompanies the reduction of the ductus arteriosus.

at the possibility that the changes in the circulation following birth are accomplished gradually and without abrupt rerouting of major blood currents.

The fact that, even though it is much greater in volume than has hitherto been recognized, the pulmonary circuit at birth is still relatively considerably smaller than it is in an adult, does not seem to offer any great difficulty. In the first place it is of the same order of magnitude as the placental circuit which has been caring for not only gaseous interchange but also food intake and waste elimination. In the second place the high red cell count and the high hemoglobin index of the fetus and neonatal infant afford an increased oxygen carrying capacity in the same manner that these conditions are known to operate in adults with certain types of congenital defects of the heart. Finally, the infant does not indulge in physical activities of a type which put a sustained excessive demand on oxygen intake until

ample time has elapsed for readjustment to postnatal conditions. There is, in brief, no functional exigency that forces us to postulate a violent postnatal increase in the volume of the pulmonary circulation. That there is some immediate acceleration of flow under the influence of the massaging effect of respiratory movements seems highly probable. But the radical increase in the volume of circulation necessary even to approximate an equalization of left with right atrial intake must await the gradual enlargement of the pulmonary channels in response to functional activity. Just how long a time elapses before such equalization takes place we can know with exactness only when there are available critical pressure determinations for both fetal and neonatal circulation. There are already known, however, several facts which fit together to give us a suggestive picture. These are:

1. The closure of the ductus arteriosus is a gradual process depending upon histological changes resembling those of endarteritis obliterans (Schaeffer,¹¹ 1914). Commencing at the time of birth there is a gradual reduction in the bore of this vessel culminating in obliteration of its lumen not earlier, on the average, than six to eight weeks after birth (Scammon and Norris,¹² 1918). This progressive occlusion of the ductus arteriosus by a process as characteristic and regular as the prenatal growth of the cardiac septa,* would tend to aid in the gradual enlargement of the pulmonary circulation by diverting a progressively greater amount of blood to the lungs.

2. In the heart of an unborn term fetus examined under water, the valvula foraminis ovalis does not lie stretched in close apposition to the interatrial septum but balloons out toward the left atrium in a position which shows the influence of the prenatal blood flow from right to left (Fig. 1). This characteristic configuration is lost gradually during the first postnatal month in a manner strongly suggestive of a gradual cessation of interatrial flow paralleling increase in pulmonary return. Measurements of the functional interatrial orifice made with a calibrated cone show a progressive reduction in its size following the "taking up of the slack" in the valvula and culminating with complete anatomical closure rarely earlier than from six to nine months after birth. Furthermore a distinct histological alteration in the valvula accompanies these changes. At birth the valvula is composed almost entirely of muscle with just a thin endocardial investment. Beginning two to three months after birth there is an exceedingly rapid increase in fibrous

*That the occlusion of the ductus arteriosus is an active process is indicated by the fact that prodromal histological changes in its intima are not uncommonly recognizable in fetuses which died without breathing and consequently never were subjected to the influence of postnatal living conditions, and further by the fact that the ductus sometimes closes in individuals with congenital defects of the heart of a type in which the persistence of the ductus arteriosus would obviously increase the chances of survival. Its frequent persistence in aortic or pulmonary stenosis seems to indicate merely that it is possible for a blood current of sufficient power to offset the normal tendency to closure. Failure of the ductus to become obliterated in the absence of some obvious cause is extremely rare, much rarer than primary developmental arrests of the cardiac septa.

tissue which by six months has increased 500 to 600 per cent, while there is in the same period no appreciable increase in the muscle tissue (Patten,⁶ 1930). These changes at the foramen ovale clearly imply its gradual abandonment concurrently with the decrease in bore of the ductus arteriosus and the increase in pulmonary circulation.

3. The lungs of neonatal infants coming to autopsy characteristically show incomplete inflation. The lungs appear to come into full functional activity but gradually, the atelectatic areas becoming progressively smaller until complete inflation is reached normally about the third postnatal week.

4. The high red cell count and the high hemoglobin index characteristic of the fetus and neonatal infant rapidly decrease during the first month after birth (Japha,² 1908). This decrease probably parallels the increase in volume and efficiency of the pulmonary circulation.

5. The portion of the aorta between the origin of the left subclavian artery and the entrance of the ductus arteriosus ("isthmic portion") which, in the fetus, is characteristically narrowed (see Fig. 3) takes two months or more to widen to the bore of the aorta below the ductus. This seems indicative at once of a gradual cessation of ductus contribution to aortic current, and of a gradual gain in the power of the blood stream delivered by the left side of the heart to the aortic arch proximal to the narrowing. This in turn must depend upon the progressive increase of pulmonary return to the left atrium.

With full recognition that until pressure determinations are available for the fetal and neonatal circulation the evidence is incomplete, it can nevertheless be stated that all the facts now available point to the conclusion that the changes in circulation following birth are gradual rather than abrupt. As nearly as it can be sketched out at present the transition from fetal to neonatal circulation seems to occur thus: By the time of birth the fetal pulmonary circulation has developed to a point such that it is capable of supporting life as soon as the lungs are ventilated. After birth, under the stimulus of the functional activity of the lungs, the pulmonary circulation rapidly gains in power and volume. It is quite possible that the progressive reduction of the ductus arteriosus is normally a contributing factor in this increase in pulmonary circulation, but the increase can be—and not infrequently is—attained in cases where the ductus remains unclosed. By the end of the first or the beginning of the second postnatal month the pulmonary return to the left atrium has reached approximate equivalence with the right atrial return. When this has occurred, the foramen ovale falls into disuse as an equalizing short-cut between the pulmonary and systemic sides of the circuit. Its anatomical obliteration follows leisurely in the wake of its functional abandonment.

In the absence of actual structural defects of the valvula which make it inadequate to occlude the foramen ovale, delay in its fairly complete closure should be regarded, not as a cause of circulatory incompetence, but as a result of failure successfully to attain the new functional equilibrium characteristic of postnatal life. For example, practically all of the many recorded cases of true congenital pulmonary stenosis show retention of a widely open foramen ovale. Failure of absolutely complete fibrous adhesion of a functionally competent valvula should be sharply distinguished from a freely open condition of the foramen ovale. Failure of complete adhesion is very common (± 20 per cent of all adults) and appears to be of no functional significance provided the valvula completely covers the septal orifice, and there is no complicating abnormality elsewhere in the cardiovascular mechanism.

The establishment of the new functional balance in the heart and the closure of the fetal communications between the pulmonary and systemic circuits carry in their wake changes in the relative development of right and left ventricular musculature. In the fetus with its open ductus arteriosus the load of the systemic circuit is shared by the right and left ventricles, and their muscular walls are of about the same thickness, although the total bulk of the right ventricle is a little greater because of its slightly greater capacity. By three to four months after birth the left ventricular musculature has overtaken the right in response, first, to the progressively increasing return from the lungs; then, as the fetal passages become closed, to the added stimulus of the long systemic route over which the blood must be pumped by the left ventricle alone. In response to this added load the left ventricular weight begins to climb steadily above that of the right, until its full adult degree of preponderance is reached somewhere around the seventh year (Müller,⁵ 1883, Gross,¹ 1921).

SUMMARY

On the basis of the evidence at present available, the changes in circulation which take place following birth may be summed up as follows:

1. Current conceptions as to the occurrence at the moment of birth of an abrupt rerouting of the blood in the heart and great vessels rest on insufficient evidence.
2. There is an increasing reason to believe that the volume of blood circulating through the lungs at the close of fetal life is adequate to care for the respiratory demands of the newborn infant as soon as the lungs are properly ventilated, and that no radical circulatory upheaval occurs at the time of birth.
3. In the neonatal period, with the assumption of respiratory function, the volume and power of the pulmonary circuit gradually in-

crease, bringing about, by the close of the first month, a new functional balance in intracardiac pressure.

4. It is probable that under normal conditions the progressive closure of the ductus arteriosus accelerates the enlargement of the pulmonary vessels following birth, but there are many cases on record where a normal pulmonary circulation has been established without closure of the ductus.

5. With the establishment of the new interatrial equilibrium brought about by increase in pulmonary circulation the foramen ovale falls gradually into disuse.

6. Anatomical obliteration of the foramen ovale follows slowly in the wake of its functional abandonment. Provided the valvula foraminis ovalis competently covers the foramen ovale, failure of the valve completely to fuse to the septum is no functional handicap as long as there is not an intercurrent disturbance elsewhere in the cardiovascular mechanism or in the lungs. This fusion is incomplete, leaving what might be termed a "probe-patency" in about 20 per cent of all adults. Functional incompetence of the valvula by reason of defective development, which should be clearly distinguished from "probe-patency," is as uncommon as other cardiac anomalies.

7. Failure of the ductus arteriosus to close within the normal time range is to be regarded as a symptom rather than a cause of circulatory disfunction. Instances of the ductus remaining unclosed in the absence of abnormal conditions which force the maintenance of a blood current through it are exceedingly rare.

8. Following the increase in pulmonary circulation and the closure of the fetal blood passages there is a gradual increase in the left ventricular musculature to equal the right at about three to five months, acquire a definite preponderance by the second year, and its full adult degree of preponderance by about the seventh year.

REFERENCES

1. Gross, L.: *The Blood Supply to the Heart*, New York, 1921, Paul B. Hoeber.
2. Japha, A.: *Diseases of the Blood and of the Blood Preparing Organs*. English translation of Pfaundler and Schossmann, "Diseases of Children," Philadelphia and London, vol. 2, pp. 131-168, 1908, Lippincott.
3. Kellogg, H. B.: *The Course of the Blood Flow Through the Fetal Mammalian Heart*, *Am. J. Anat.*, 42: 443, 1928.
4. Kellogg, H. B.: *Studies on the Fetal Circulation of Mammals*, *Am. J. Physiol.*, 91: 637, 1929.
5. Müller, W.: *Die Massenverhältnisse des menschlichen Herzens*. Hamburg u. Leipzig, 1883, Leopold Voss.
6. Patten, B. M.: *The Normal Closure of the Foramen Ovale*. Paper in Preparation.
7. Patten, B. M., Sommerfield, W. A., and Paff, G. H.: *Functional Limitations of the Foramen Ovale in the Human Fetal Heart*, *Anat. Rec.*, 44: 165, 1929.
8. Patten, B. M., and Toulmin, K.: *Certain Measurements of the Fetal Heart and their Significance*. Paper in preparation.

9. Pohlman, A. G.: The Course of the Blood Through the Heart of the Fetal Mammal, with a Note on the Reptilian and Amphibian Circulations, *Anat. Rec.*, 3: 75, 1909.
10. Reid, J.: Injection of the Vessels of the Fetus to Show Some of the Peculiarities of Its Circulation, *Edin. Med. Surg. J.*, 43: 11, 1835.
11. Sabatier, R. B.: (Cited by Pohlman.) *Traité complet d'anatomie*, 2: 493, 1791.
12. Scammon, R. E., and Norris, E. H.: A Statistical Summary of the Data on the Time of Obliteration of the Foramen Ovale, Ductus Arteriosus, and Ductus Venosus in Man, *Anat. Rec.*, 15: 165, 1918.
13. Schaeffer, J. P.: The Behavior of Elastic Tissue in the Postfetal Occlusion and Obliteration of the Ductus Arteriosus (Botalli) in *Sus Scrofa*, *J. Exper. Med.*, 19: 129, 1914.

THE REVERSAL OF FLOW IN THE CARDIAC VEINS*†

OSCAR V. BATSON, M.D., AND SAMUEL BELLET, M.D.
PHILADELPHIA, PA.

THE problem of the actual irrigation of the myocardium has been overshadowed by the study of the anastomoses of the coronary arteries. Interarterial connections are significant only in cases of partial or total occlusion of a single coronary artery; their significance completely disappears in double coronary occlusion. With this condition, with the arterial supply shut off, patients can live for a number of months, perhaps for two years.^{4, 19, 22, 34, 44} Hypotheses, centering about irrigation by the Thebesian veins, or about anastomoses with the vasa vasorum, have been advanced to account for this persistence of life. The hypotheses are unsatisfactory either because they have been arrived at by a process of exclusion (which, as we shall show, has not been completely carried out), or because they are based upon experiments with isolated hearts.

In our study we have sought to obtain definite, direct evidence in the intact animal toward answering the question: How are the myocardial capillaries irrigated?

To make clear our point of view in discussing these experiments we will first present our concept of the vascular systems of the myocardium. In the light of our own experience in the study of anatomical specimens, as well as in the light of our experiments, we have essayed the following correlation and interpretation of the facts of the myocardial circulation.

THE MYOCARDIAL CIRCULATION

The exact anatomical peculiarities of the vascular bed of the heart are still not fully determined. The elementary notion of a small artery ending in a capillary bed and this in turn drained by a small vein is here entirely out of place. To begin on the arterial side, the question of anastomoses has been most confusing. These anastomoses have been found, confirmed, denied, and confirmed again. At present the work of Spalteholz,^{38, 40} Nussbaum,³¹ and of Gross⁹ definitely establishes the presence of these anastomotic connections. The exact maximum of size of these connections we feel to be still in doubt because the intrin-

*From the Department of Anatomy, Graduate School of Medicine, and from the Robinette Foundation, University of Pennsylvania.

†Preliminary reports of this paper were presented before the meeting of the Interurban Medical Society, Philadelphia, April 5, 1930, and before the meeting of the American Association of Anatomists, Charlottesville, Va., April 17, 1930. An abstract of the latter presentation appeared in the *Anatomical Record*, 45: 206, 1930.

sie contractility and the passive distensibility of the vascular tree interfere with determining the size of the communications from anatomical specimens, whether these be injected preparations or sections.

In addition to these intracardiac anastomoses we must also consider the extracardiac ones. The paper by von Langer²² gives what seems to be the most complete account of these. In considering occlusion of the coronary arterial ostia, the most important extracardiac connection seems to be the communication between the coronary arteries and the bronchial arteries through the capillaries of the vasa vasorum of the first part of the aorta. In some of the reported cases the occlusion of the ostia of the coronary arteries has been accompanied by an obliteration of the lumina of the arteries for some distance from their origin. In these cases the extracardiac anastomoses with the bronchial arteries could not operate. The capillary bed in the region of the sinuses of Valsalva is so small that it does not seem possible that such anastomoses could nourish more than a small fraction of the myocardium. No doubt the extracardiac supply of the human heart could be restudied with profit, especially if such studies were correlated with the comparative anatomical studies of Grant and Regnier.⁷ Since the lumina of nonfunctioning vessels are commonly obliterated, even when the vessels are not involved in a pathological process, it would be most helpful to have a complete description of the entire coronary arterial tree in the cases of double coronary occlusion. Arteriovenous anastomoses, to our knowledge, have not been recognized under that classification⁸ in the heart, except by Nussbaum.³¹ He believes that this system, which he found in the epicardium, serves to transmit blood from the arteries to the veins during systole when the capillaries are contracted. The general distribution of the arteriovenous anastomoses was first described by Hoyer.¹³ The widespread presence of this connection is now well established. It is not surprising to find this anastomosis developed in the heart.

On the venous side we may divide the larger vessels into those which empty into the coronary venous sinus and those which empty into the right atrium directly. The coronary sinus has valves, the veins which empty directly into the right atrium do not. Since the influence of the valves of the coronary venous sinus can be discounted^{32, 46} in 97 per cent of the cases, there does not seem to be any essential difference between these two classes of veins. Grant and Regnier⁷ think that these various veins are present as an incomplete transformation of the primordial extracardiac venous drainage. The congenital anomalies of connection of the veins do not concern us in this present discussion,

*Halpert¹¹ reports what seems to be an unique case of a cardiac arteriovenous aneurysm. "The anastomosing loop shows a microscopic structure intermediate between an artery and a vein. Anatomically, the malformed vessels constitute a direct and relatively wide communication between aorta and right atrium; it is remarkable that such a striking abnormality was not associated with obvious disturbance of the heart during life."

for they too are the persistence, for the most part, of remnants of an extracardiac drainage. Intervenous anastomoses are of large size and of frequent occurrence. They are readily recognized with the naked eye.

There is a third group of vascular channels, the components of which have commonly been considered as unrelated structures, or these components have been divided into more groups than we feel is warranted. In fact, a group classification is rarely used. These channels were recognized in part and described by Vieussens in 1706⁴³ and by Thebesius in 1708.⁴¹ Other varieties of the channels have been described by von Langer,²³ Lannelongue,²¹ and others. Some observers, who have not seen all of the subtypes, have denied the existence of certain of them. This has added to the confusion. It seems to us to be significant that the multiplicity of terms and of descriptions sprang up at a time antedating the study of the embryology of the heart. Considering the work of Minot,²⁹ of Lewis²⁵ and of Grant and Regnier⁷ on the development of the sinusoids of the heart the conclusion seems compelling that these variously described channels of the adult heart represent various stages in the evolution of the embryonic (and comparative anatomical) sinusoidal system of irrigation of the myocardium. Lewis,²⁵ believing that he found obliteration of some of the sinusoidal vessels in the embryo, thought that the endothelial channels might be formed in part by ramification of new vessels. Grant and Regnier,⁷ on the other hand, have been unable to confirm this obliteration of the sinusoidal channels. We fail to see the analogy between the vasa vasorum and the endocardial vessels suggested by Lewis, and are of the opinion that all of the vascular passages of endocardial origin are modified sinusoids. According to this conception, based on development, on comparative anatomy, and on comparative physiology, all of the endocardial channels in any chamber: the blind pits, the communicating pits, the branched channels, the arborizing channels and those channels connecting with the capillary bed, are all parts of the sinusoidal system. It is true that certain of these have been called Thebesian veins (the *venae cordis minimae* of the BNA.) but there has been no agreement among authors as to what should be included under this term, and we have found authors using the term in a restricted sense in one paper and in an amplified sense in another. Some investigators, Pratt,³⁴ Wearn⁴⁴ and Kretz,¹⁹ for example, feel that in cases of coronary occlusion the direction of flow is away from the cavities of the heart. In view of the embryological and comparative anatomical background of these vessels, and in view of their uncertain physiology, we feel that the term "vein" should be dropped, that the entire group of crypts and vessels should be referred to as the sinusoidal circulation of the heart, or if this does not meet with approval, to alter the term from *venae cordis minimae* (BNA) to *vasae cordis minimae*. In

this paper we shall refer to all vessels of endocardial origin as sinusoidal vessels. We shall not use the term, Thebesian vein, which we consider unsatisfactory.

So far as the embryology of the vessels of the heart has been worked out, the various circulations appear in the following order: The irrigation of the myocardium is first accomplished by the sinusoidal circulation; next the veins grow out and arborize; last of all, the arteries grow out and meet the capillary ramifications of the veins, and all three, sinusoids, veins, and arteries, become intimately connected through the developing capillary bed. So much of our knowledge of embryology has been accomplished through the study of stereotyped stages that we are inclined to overlook embryonic physiology. In the rabbit embryo, the veins exist as an independent system for days. With the pressure changes at their ostia, with the movement of the heart into which they are distributed, and with the presence of blood in their lumina, we feel that a flow and ebb circulation takes place in the veins during this period of their independent existence. This flow and ebb no doubt also occurs in the arteries before they join the veins but, because of the greater pressure, the degree of flow and ebb is probably less.

Considering the origin and early history of the sinusoidal system rich communications should be expected, not only with the capillaries, but also with the arteries and veins. Both Lewis²⁵ and Grant⁶ feel that some of the capillaries are formed by a reduction in size of the sinusoidal channels. The connections with the veins have long been recognized and recently have been well demonstrated in anatomical preparations of the heart of the sheep by Grant and Viko.⁸ Connections between the arteries and the sinusoids were demonstrated by injection experiments with coarse masses by Abernathy in 1798.² Mettier, Zschiesche and Wearn²⁸ prepared anatomical specimens by corrosion which show these vessels connecting the arteries and the sinusoids. We propose to call these two (at present unnamed) connections respectively, sinusoidovenous and sinusoidoarterial anastomoses.

In summary of the foregoing review we present Fig. 1, which shows in diagram form our concept of the anatomical facts and surmises of the myocardial circulation.

The lymphatic vessels have not been included in this discussion because their drainage is extracardiac. We have seen one incomplete specimen (in the dog) in which the possibility of the connection of a large lymph vessel with the veins could not be ruled out, but if this be present it is certainly the exception.¹⁶ The amount of fluid leaving by these passages during perfusion of a heart, so far as we know, has not been determined. Considering the richness of distribution and the great size of the channels, this quantity must be quite large. In-

deed, Pratt³⁴ has suggested that the lymph channels may be concerned in the myocardial nutrition.

The study of the anatomical size and distribution of the components of the myocardial circulation by customary means is open to all the difficulties and objections encountered elsewhere in the animal organism, as well as to one peculiar to the heart. The passive distensibility of vessels has already been mentioned as well as their intrinsic contractility. We recognize, especially as a result of the work of Krogh²⁰ and of Richards,³⁶ that certain vessels may be temporarily contracted to the point of obliteration, while neighboring ones may be carrying a full stream of blood. This intrinsic contractility of vessels in localized areas, while it has not been specifically demonstrated in the heart, is no doubt active there and may explain in part some of the discrepan-

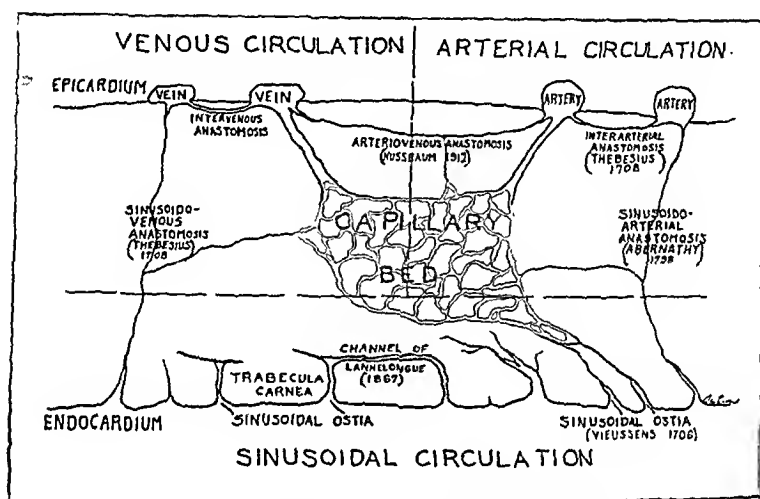


Fig. 1.—Diagram of the myocardial circulation. This diagram is based upon the embryological origin and the adult distribution of the vessels and the terminology employed is compatible with these points of view and with the terminology generally employed in the vascular system. In development the endocardial sinusoidal system develops first; the epicardial venous vessels develop next, and finally the epicardial arterial vessels develop and join the other two, forming a common capillary bed. The endocardial or epicardial origin of the vessels as well as their various modes of interconnection are indicated in the diagram.

Sinusoidal ostia are present in all four chambers of the heart.

Intervenous anastomoses have long been common knowledge. They are obvious with the naked eye.

Sinusoidovenous anastomoses have been recognized by Thebesius (1708),⁴¹ Verheyen (1712),⁴² Lanciscus (1740 [posthumous]),²³ von Haller (1786),¹⁰ Abernathy (1798),² Bochdelak (1868),³ (von Langer (1880),²³ Pratt (1898),³⁴ Nussbaum (1912),²¹ Kretz (1927),¹⁰ Wearn (1928)⁴⁴ and Grant and Viko (1929).⁵

Sinusoido-arterial anastomoses were described by Abernathy (1798)² and by Wearn (1928).⁴⁴

Arteriovenous anastomoses were described and figured by Nussbaum (1912)²¹ and *interarterial anastomoses* are reported by Thebesius (1708),⁴¹ von Haller (1786),¹⁰ Morgagni (1761),³⁰ Senac (1749),³¹ Caldani and Caldani (1810),⁵ Krause (1879),¹⁵ Jamin and Merkel (1907),¹⁵ Spalteholz (1907)²⁸ and (1924),⁴⁰ and by Gross (1921).⁹

Sinusoidocapillary connections are recognized by Vieussens (1706)⁴³ Thebesius (1708),⁴¹ Winslow (1776),⁴⁵ Verheyen (1712),⁴² Lanciscus, (1740),²⁴ Bochdelak (1868),³ Henle (1880),¹² Hyrtl (1884),¹⁴ Langer (1880),²³ Gross (1921),⁹ and Grant and Viko (1929).⁵

cies obtained through the study of injected specimens. In the heart, in addition to the difficulties met with elsewhere in injecting the vessels for study, the vascular bed is constantly modified by the contrac-

tion and relaxation of the muscle itself. In dead hearts, after the effect of rigor mortis has disappeared, post-mortem changes have altered the distensibility of the vessels and have also impaired the integrity of their walls. Fixation and subsequent treatment further alter the validity of size determinations.

Experiments with perfused hearts are open to the objection that the heart is not actually performing work.* The vascular tree is being deformed by the contraction of the myocardium, but the resistance to the outflow of vessels is not present. This type of experiment has been most useful, however, in indicating that, with vessels conducting fluid in a given direction, the heart beat can be maintained. Pratt has shown,³⁴ for example, that the heart beat can be maintained by irrigation of the sinusoidal vessels and also that the beat can be maintained for an even longer period by irrigation of the coronary veins. Considering the absence of adequate valves in the cardiac vascular system and considering the connections indicated in Fig. 1, this is readily understandable; for, as we pointed out earlier, the capillary bed is the essential part of the circulatory system. It must be here emphasized, however, that these experiments demonstrated the possibilities of perfusion in certain directions, without indicating that these directions of flow actually occur in the intact organism. In the cases of double coronary artery occlusion, Wearn,⁴⁴ Leary and Wearn,²² and previously Pratt³⁴ and Kretz¹⁹ have advanced the explanation that the capillary bed received blood entering the sinusoidal vessels from the heart chambers. Leary and Wearn state: "The only adequate explanation of the ability of these patients to live and work rests upon a belief that the Thebesian veins have supplied the compensatory circulation necessary for the functioning of the heart muscle." This conclusion seems to be commonly arrived at by the process of exclusion; however, this mode of irrigation has never been demonstrated in the intact animal.

With these occlusion cases in mind, as well as the suggested explanation, we decided to approach the problem directly by trying to follow the course of particles injected into an intact animal. In order to eliminate the coronary arteries from the field of distribution we proposed to introduce particles into the systemic venous circulation, of such a size that they would be filtered out by the lung capillaries. This gave us the opportunity to investigate all of the vessels having ostia in the right side of the heart. Any particles appearing in the myocardial circulation would of necessity have entered through these ostia, ostia which include the openings of both the venous and the sinusoidal circulation.

*To quote Pratt³⁵, in discussing his own experiments: "Too much must not be inferred from such a demonstration for the heart is working against practically no resistance."

In retrospect, we can divide our experiments into three groups, which follow each other chronologically. A sufficient number of experiments from each group will be here reported in detail to show the character of our findings. Our first experiments were concerned with finding a suitable injection material. Dogs were used as experimental animals.

FIRST GROUP OF EXPERIMENTS

Unfortunately, there are no particles which have been standardized for use in injection experiments. For our first experiment we tried the glass particles which are sold for the purpose of "frosting" objects for decoration. These are smooth glass particles, like beads without perforations, with a diameter ranging from 200 to 600 micra.

EXPERIMENT 1.—October 25, 1928. Dog under amytal anesthesia. The right external jugular vein was exposed and a cannula ligated in place. A 50 c.c. syringe was filled with a "suspension" of the above described glass beads in normal saline. These were rapidly injected to prevent settling. This was repeated (total 100 c.c.). The animal expired seven minutes after the termination of the injection.

Findings.—Roentgenograms of the thoracic viscera showed extensive filling of the pulmonary vascular tree. Glass bead shadows were found singly and in clusters in the nonseptal portion of the right heart and in the interventricular septum. No bead shadows were seen in the nonseptal portion of the left heart.

Direct Examination.—The heart, which was markedly dilated on the right side, was opened and examined grossly, and with the binocular microscope (Greenough type). Large masses of fibrin, containing enmeshed glass beads were found in the right ventricle. These strands were especially numerous in the crypts between the columnae carneae. No beads or fibrin strings were found in the left heart. In two instances beads were found within sinusoidal orifices in the right ventricle.

Discussion.—The difficulty of retaining the beads in suspension suggested that a lighter particle would be more suitable. The dilated right heart and the filled pulmonary vascular tree indicated that death was due to the pulmonary embolism with the resulting fall of pressure in the left heart and in the coronary arteries. This condition then, simulated to a great degree an acute coronary occlusion.

EXPERIMENT 2.—November 1, 1928. Because of its availability in graded sizes we decided to use carborundum powder in our next experiment. We used the grade FFF, which was prepared by repeated washing with saline solution. After each washing the finer particles were removed by decantation.

Procedure.—With the dog under amytal anesthesia 100 c.c. of FFF carborundum powder suspension were injected into the right external jugular vein. Within two minutes after the beginning of the injection breathing ceased, and the animal went into an extension rigor. The heart beat could not be heard. The chest was immediately opened, the great vessels were ligated, and the heart and lungs were immediately removed.

Findings.—The lungs showed a patchy grey discoloration which on close inspection was seen to be carborundum. Grossly, the veins of the entire heart contained carborundum. Inspection of these vessels under magnification and dissection showed the coronary venous sinus and its tributaries to be well filled. On opening the heart, the right side was found filled with a large, firm, carborundum containing clot. The carborundum was found chiefly on the periphery. Some extensions of the clot into crypts came loose when the clot was washed out. The

ostia of the sinuoids were well filled with the particles. The specimen was fixed in formaldehyde solution and then cleared by the Spaltholz method.³⁰ Upon examination of the cleared specimen the findings noted above were confirmed. Carborundum was not found in the left heart.

Discussion.—The finding of particulate matter in the superficial cardiac veins indicated the surprising fact of a reversal of flow in these vessels. We determined to investigate the influence of the massive clot and the dilated right side of the heart on this reversal. It was considered highly possible that the conditions of the experiment were so unusual that they were not only outside of normal circulatory conditions but also outside of pathological ones. Further, the introduction of the material with a syringe so near the heart might have caused a direct injection.

EXPERIMENT 3.—November 6, 1928. The conditions of the last experiment were duplicated except that particulate matter was introduced into the right femoral vein in order that the venous pressure might be less disturbed. The findings were in all respects the same, including the finding of carborundum in the coronary veins. Apparently the reversal of flow in the preceding experiment had not been caused by the pressure of injection.

Our next experiments were directed toward finding a means of eliminating the massive clots formed by the carborundum.

SECOND GROUP OF EXPERIMENTS

It was suggested to us by Dr. G. M. Higgins of the University of Minnesota, that colloidal graphite might be a satisfactory substance, and that, in his experience, clots did not form when it was used. We found that the particles of the colloidal graphite were too small for our purposes, but we decided to try commercial flake graphite.

EXPERIMENT.—April 10, 1929. Fine, flake natural graphite commercially obtained was prepared with physiological salt solution. The finer particles were removed by decantation and by the use of a centrifuge. A medium sized dog under amytal anesthesia was used. A gravity tube ligated in the right femoral vein was used for the injection. The graphite suspension was introduced at a maximum pressure of 12 centimeters of water. Twenty cubic centimeters were introduced after which, either due to a plugged cannula or to the failing heart no more would run in.

Findings.—No graphite was seen upon opening the abdomen. Upon opening the thorax the right side of the heart was found to be distended and firm. No graphite could be seen grossly in the lungs. On opening the heart dense clots were seen in both sides. Graphite was found only in the right side. Graphite was found in the coronary venous sinus and in the coronary veins. Graphite was found in smears from the lungs. None was found in the clot from the left heart, and none was found in smears of the splenic pulp.

Discussion.—The graphite seemed to be a better substance to inject than the carborundum, but it caused coagulation in its commercial flake form. We decided to continue the use of graphite but to try the use of an anticoagulant.

The effect of the injection of peptone solution was tried but the results were not completely satisfactory. Following this we turned to heparin.

Considering the acute nature of our experiments we felt that a smaller dose than recommended would probably suffice.

EXPERIMENT.—April 27, 1929. Dog was placed under amytal anesthesia. A gravity cannula was ligated into the right femoral vein. Fifty milligrams of heparin

per kilogram of weight were injected intravenously, and thirty minutes were allowed to elapse. The absence of the clotting of the blood was determined by making skin incisions and mixing graphite with the exuding blood. Thirty-five cubic centimeters of a graphite suspension were injected at a pressure of 110 mm. of water. Respiration ceased in two minutes.

Findings.—The cardiac blood was not clotted. Graphite was abundantly present in the coronary veins and in the cardiac veins.

Discussion.—In this experiment the injection of the cardiac veins was due neither to the height of the injection pressure nor to the massaging action of the clot. Up to this time the pressures present in the right atrium of the heart and in the arteries had not been determined; however, gross observation showed them to be quite abnormal. This lack of information brought us to our third set of experiments. Here we endeavored to determine these pressures in the right side of the heart, and to bring them within normal ranges.

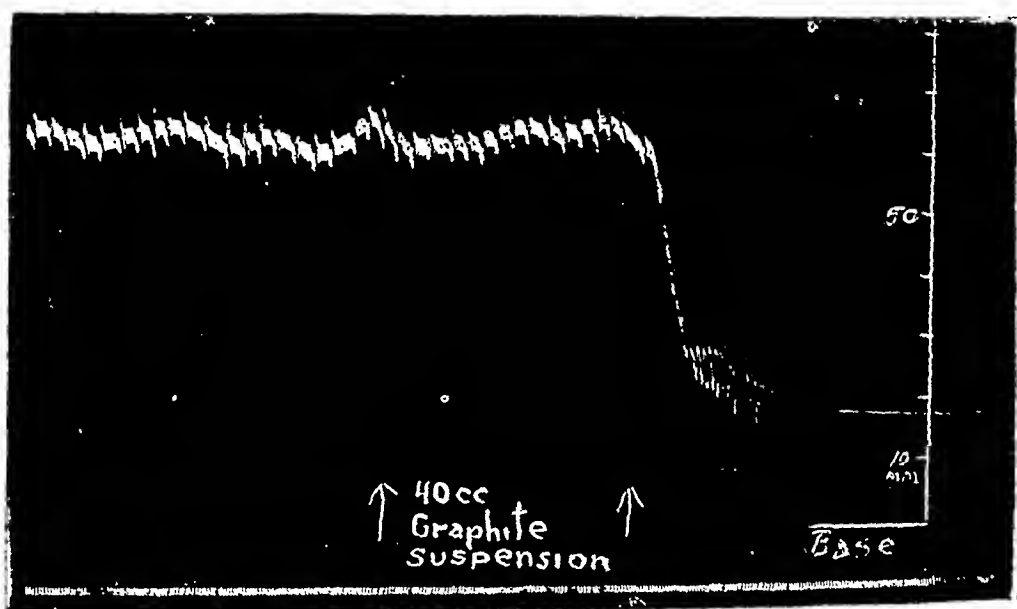


Fig. 2.—Tracing of pressure in the left carotid artery. Experiment, December 3, 1929, at the time of injection of the graphite suspension into the systemic veins.

THIRD GROUP OF EXPERIMENTS

EXPERIMENT.—Carotid pressures. December 3, 1929. The conditions of this experiment duplicated those of the one last recorded except that the necessary apparatus was arranged to record the carotid pressure. The injection pressure was 12 cm. of water. The animal ceased breathing shortly after the injection of the graphite suspension (Fig. 2). Graphite was found in the heart as in the previous experiments.

Discussion.—The figure of the blood pressure curve (Fig. 2) is characteristic of others that we obtained later. This shows the extent to which the coronary pressure was reduced and also the height of the residual pressure, in these experiments.

In order to determine the pressures in the right atrium or its superior entrance, a water manometer was used, to which a cannula long enough to reach the heart was attached.

EXPERIMENT.—December 10, 1929. Dog was placed under amytal anesthesia. A gravity injecting cannula was ligated into the right femoral vein, and heparin was

administered. A cannula, inserted into the left carotid artery, was connected to a recording manometer. The right external jugular vein was isolated. A glass tube, paraffin coated internally, as an additional precaution against clotting, was inserted into the right external jugular vein, toward the heart, for a distance of sixteen centimeters. The tube contained sodium citrate solution, and the free end was connected to the water manometer. Part of a fifty cubic centimeter quantity of a graphite suspension was introduced into the femoral vein at a pressure 5 cm. higher than the venous pressure at that point. The ensuing violent respirations caused such rapid shifts in the water manometer column that all of the levels could not be recorded. Fig. 3 indicates those readings that were recorded. Especially significant is the maximum figure of 43.5 cm. of water. The carotid tracing was in all respects similar to Fig. 1.

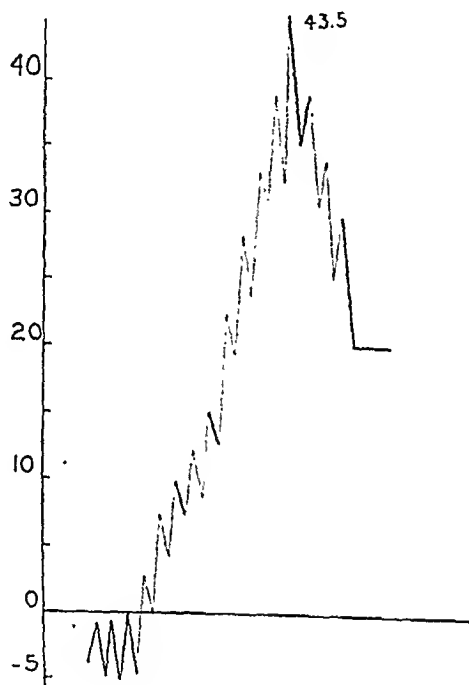


Fig. 3.—Experiment, December 10, 1929. Pressure in the right atrium during injection of a graphite suspension into the right femoral vein, toward the heart. The heavy lines indicate actual readings. The light lines are approximations. The figures are centimeters of water.

Findings.—The gross appearances of the heart is illustrated in Fig. 4. The presence of large quantities of graphite was much more obvious after the clearing of the specimen.

Discussion.—This experiment makes it clear that, in this vascular system with inadequate valves, a falling arterial pressure and an increased intra-atrial pressure results in a reversal of flow on the venous side.

As shown by Fig. 4 the particles are well distributed in veins of the left ventricle, remote from the right atrium. The question as to the minimum pressure in the right atrium necessary for this reversal was raised as well as the possibility of the direct inspection of the vascular tree.

EXPERIMENT.—December 12, 1929. Dog under amytal anesthesia. The thorax was opened by means of a saw cut splitting the sternum. Artificial respiration was carried out. Heparin was administered. The right coronary artery was ligated in

the coronary sulcus as well as two branches of the anterior descending ramus of the left coronary artery in order to produce a localized fall in coronary arterial pressure.

At this point direct inspection with a binocular magnifier, attached to a head band was attempted, in an effort to follow the direction of flow. The attempt was unsuccessful because it was not possible by this means to follow the flow in the rapidly moving heart and because localized immobilization was unsuccessful.

Next a cannula having a side outlet at 20 cm. was introduced directly into the superior vena cava. Thirty cubic centimeters of a graphite suspension were injected into the left femoral vein at a pressure 5 cm. above venous pressure.

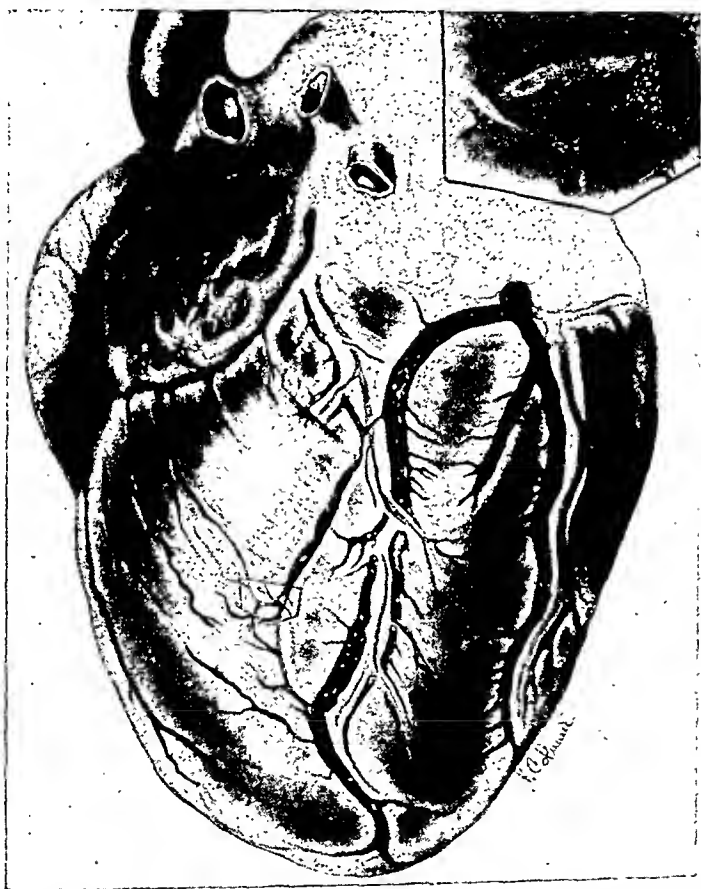


Fig. 4.—Dog's heart from experiment, December 10, 1929. Graphite particles are seen in the veins over the left ventricle. The inset shows a magnified view of the indicated area.

Pressure in the cannula in the vena cava rose to the 20 cm. outlet tube and about 10 c.c. spilled over. The outlet was closed, but the pressure did not rise above this level. The animal lived for three minutes after the graphite injection.

Findings.—The right heart was markedly dilated. The lungs contained graphite. The heart (Fig. 5) contained less graphite than the preceding specimen, but the distribution was similar.

Discussion.—The pressure here recorded, 20 cm. of blood, was much lower than the 43.5 cm. of water of the previous experiment. The difference between the two pressure readings was probably due to the opened chest. The experiment indicated that venous pressures within the range of pressures of pathological heart conditions could cause a reversal of flow in the heart veins.

The next experiment was planned so as to reduce or to eliminate the rise in intratrial pressure.

EXPERIMENT.—Dec. 19, 1929. Dog was put under amytal anesthesia. The gravity injection cannula was inserted into the left femoral vein. The right external jugular vein was isolated, preliminary to the introduction of a cannula. A large bottle partly filled with sodium citrate solution was connected by means of a syphon tube with a water manometer and a jugular cannula. The zero levels of the manometer and the syphon bottle were adjusted to coincide with the level of the right external jugular vein (Fig. 6). The animal was given heparin, and thirty minutes later 40 c.c. of a graphite suspension were introduced at an injection pressure of 5 cm. of water.

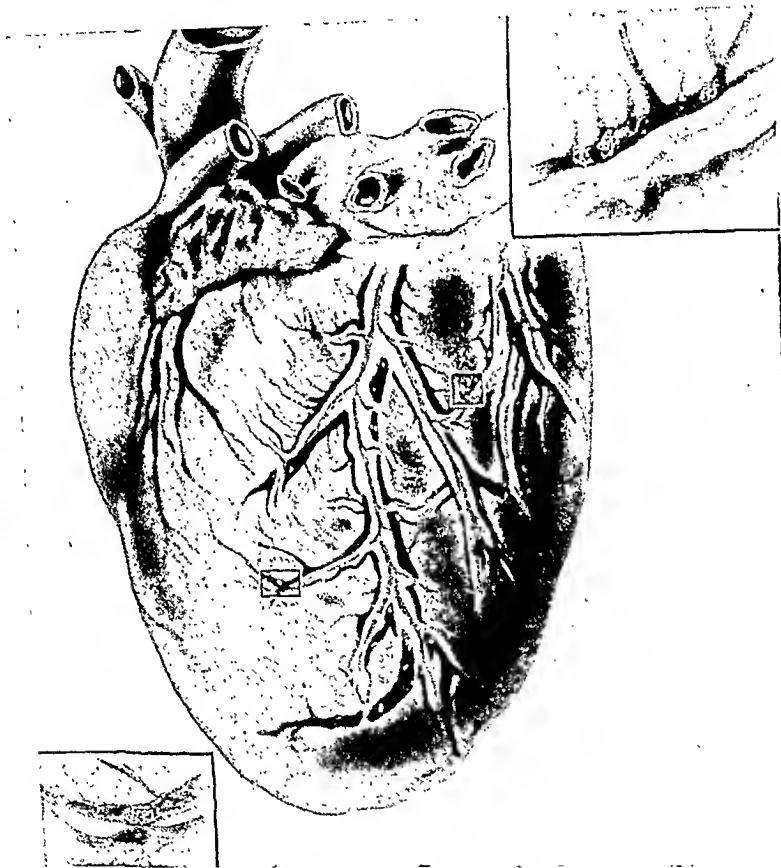


Fig. 5.—Heart from experiment, December 12, 1929. Distribution of particles indicating the extent of the reversal of flow in the cardiac veins with an intratrial pressure of 20 cm. of blood.

The pressure in the right atrium, as indicated by the manometer, rose momentarily to 11 cm. of water and then dropped rapidly to zero. (This rise may have been due to the inertia of the system, for the pressure drop to zero coincided with the arrival of the blood column in the equalizing bottle.) To relieve the respiratory embarrassment the equalizing bottle was lowered until the manometer reading stood at minus five centimeters. The breathing continued labored and the heart stopped beating.

Findings.—The thorax was opened. The cannula was found within the entrance of the left atrium. The vessels were ligated, and the specimen was removed. Graphite particles were seen in the fresh specimen in the veins accompanying the anterior descending branch of the left coronary artery (Fig. 7). This specimen was

later cleared and the further distribution of particles noted. Fewer particles were seen in this specimen than in previous ones.

Discussion.—This experiment carried out under lower pressure conditions—conditions which are within the limits of normality—shows that high pressures on the venous side are unnecessary for the injection of the veins in the presence of the falling arterial pressure.

The apparatus was modified by increasing the caliber of the tubing and shortening the length of the connections, in an effort to lessen the inertia of the system. A graphite suspension was carefully prepared, and the size of the particles was determined by the use of an ocular micrometer. The minimum diameters of one hundred measured particles ranged from 51 to 210 micra.

EXPERIMENT.—March 11, 1930. This experiment in all details duplicated the one last reported. Following the injection of 30 c.c. of the graphite suspension the pressure in the manometer did not deviate from zero. Blood appeared in the bottle, showing that the system was patent. The animal died about three minutes after the injection. The thorax was opened, the intra-atrial position of the cannula confirmed, the great vessels were ligated, and the heart was removed. Graph-

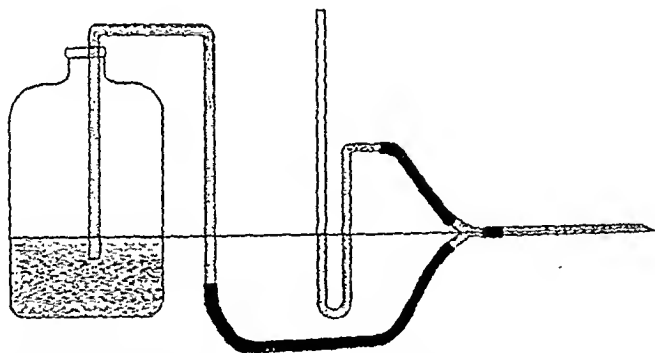


Fig. 6.—Arrangement of syphon bottle, manometer and jugular cannula in experiment of December 19, 1929. The zero level was adjusted to correspond to the level of the right external jugular vein.

ite particles were easily found in the veins. The specimen was fixed and later cleared by the Spalteholz method.³⁹

Examination of the cleared specimen confirmed the presence of the graphite particles of the largest size in the heart veins and showed the left ventricle to be free of graphite.

Discussion.—In this experiment we feel that we have removed any question concerning the reversal of flow in the veins at normal pressure levels in the right atrium, when accompanied by a fall of pressure in the coronary arteries.

It was suggested that perhaps the presence of the sinusoidovenous anastomoses would account for the particles in the veins, without a reversal of flow being present. It is true that in some of the specimens from our experiments we had noted an injection of sinusoidal vessels, but we were never able in these to establish the continuity of a chain of particles from the sinusoids to the vein. In addition, because of the large size of the particles used, because of their presence in the veins of the left heart, and because of the great quantity present in all veins in certain experiments, we did not feel that this mode of injection was a possibility. However, to answer this type of objection we prepared a suspension of graphite from very large flakes. This was injected into an animal on April 8, 1930, according to our usual technique. The heart was removed and very carefully cleared by the

Spalteholz method, using certain procedures (which will be reported by one of us elsewhere) to develop the maximum clarity of the preparation. With this specimen in its finished state it has been very easy to study the vascular distribution and the presence of particles in the entire heart. It has been possible by the use of special illuminants, an arc lamp with a thick cobalt glass filter, to obtain what amounts to a selective illumination of a differential character, for the blood vessels. By careful study of the distribution and measurement of the size of vessels, using an ocular micrometer, we were successful in finding a vein containing large particles, that was so distributed anatomically, that the presence of large anastomoses could be ruled out. The connections were of such a small magnitude, that even if they included sinusoidovenous anastomoses the passage of the particles from sinusoids to veins would not be possible. We are fully cognizant of the known extrinsic

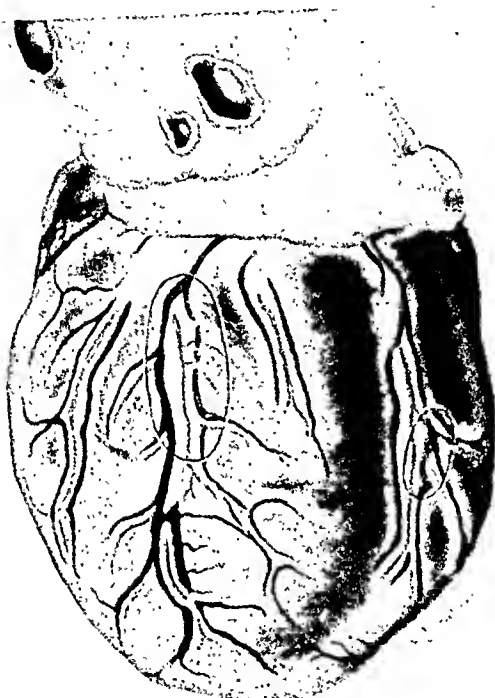


Fig. 7.—Heart from experiment of December 19, 1929. The reversal of flow in the cardiac veins is shown by the distribution of the graphite in the veins. The intra-atrial pressure reached a maximum of 11 cm. of water.

factors which alter the size of vascular lumina, we believe in the presence of an intrinsic alteration, and we appreciate the alterations, especially shrinkage of vessels caused by fixation, dehydration, and clearing, but we feel that the discrepancies in sizes here are too great to permit of any explanation, other than that the particles traveled into the vein in a manner exactly reverse to that which the blood is accustomed to follow. The largest particle is 800 micra by 1200 micra in this vessel and all of the arborizing (Fig. 8) vessels have been traced until their greatest internal diameter is less than one hundred micra. Fig. 8 is a composite illustration, made from camera lucida drawings. The diameters have been corrected to scale. The original drawings were made by rendering one tube of a Greenough type binocular vertical and attaching a camera lucida to this vertical tube. The other eye piece of the microscope was equipped with an ocular micrometer so that the measurements could be made. The illumination has already been mentioned. Focusing was accomplished by moving the specimen. It was necessary to make a series of draw-

ings because the vessel in question, one of the anterior cardiac veins, was followed from its ostium in the right atrium to its 200 micra anastomosing channels at the apex and then followed along the anastomotic vein until the direction of flow normal to this vein became apparent from the angles of fusion of the entering vessels.

PROBABLE MODE OF IRRIGATION IN CORONARY ARTERY OCCLUSION

Irrigation of the myocardium compatible with life, by venous blood, is not unknown (Abbott¹). Furthermore, those that maintained that the sinusoidal circulation supplied the mode of irrigation in cases of coronary artery occlusion were offering an explanation that depended in part upon the use of blood from the right heart. It is easy

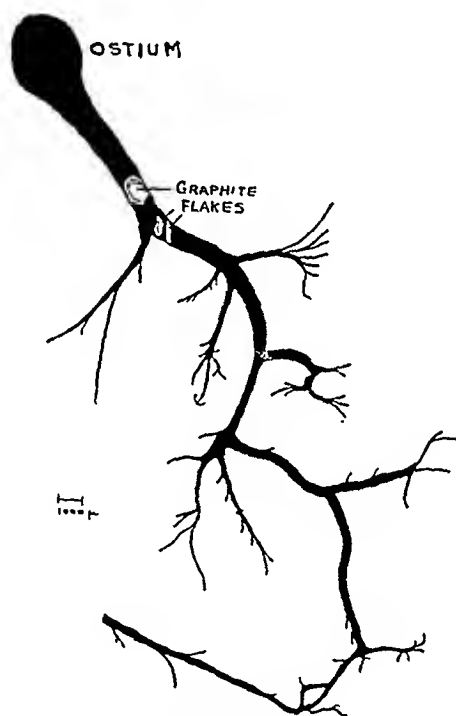


Fig. 8.—Camera Lucida drawing of the lumen of an anterior cardiac vein from the specimen obtained from the experiment of April 8, 1930. All of the connecting vessels with a diameter in the cleared specimen of more than 100 micra are delineated. The intervenous anastomosis in the lower part of the figure has a diameter of 200 micra. The largest graphite flake measures 800 by 1200 micra.

to understand how the myocardium can be maintained by venous blood when we recall that the oxygen tension of venous blood ranges from 60 to 70 per cent while the figure for arterial blood is 95 per cent.

In cases of occlusion of the coronary arteries we suggest that the blood passes into the veins at the time of atrial systole, it may flow in part through sinusoidovenous anastomoses into the ventricles as well as into the capillary bed. We believe that this blood is forced from the capillaries with the onset of ventricular systole. It is entirely possible that this blood reenters the heart chambers by two sets of channels, the veins and the sinusoids. The time periods of the heart cycle.

the rate of blood flow, and the length of the vascular bed make this flow and ebb explanation plausible. In some of our specimens, we have seen an injection of the sinusoidal ostia also. This may mean that blood also enters the capillary bed by these channels. Up to the present we have not endeavored to alter our experiments to evaluate the exact relationships between these two systems. There need be nothing incompatible in the idea that the capillary bed is supplied in both manners; although, if, as it is commonly thought, the ventricular sinusoidal vessels are filled during systole, it seems to us difficult to visualize how the capillary bed can be irrigated at this time when external pressure is greatest.

By considering the connections of the vascular system of the heart (Fig. 1) and by considering the absence of competent valves, the irrigation of the heart in coronary artery occlusion seems to us to become a simpler problem. The blood undoubtedly flows from vessels of greater pressure to vessels of lesser pressure. We realize that we have not determined the exact pressures involved, because we have not determined the effective pressures, i.e., the differences between the intra-atrial pressures and the intrathoracic pressures, under the conditions of our experiments, nor have we obtained intraventricular pressures to accompany these. These pressures no doubt will have to be determined and carefully compared before all of the ramifications of this problem are clear.

Again we mention the work of Pratt in 1898, showing that irrigation through veins was adequate for maintaining the perfused heart, and we also note that he considered this of sufficient importance to give it a subheading in his report. Porter,²³ in observing the hearts of cats and dogs recovering from fibrillary contractions, believed that this occurred through irrigation of the heart through the sinusoidal vessels and the coronary veins which were in a position peculiarly well adapted to function as a result of the pressure changes taking place in the ventricles during this state.

CLINICAL IMPLICATIONS

The myocardial capillary bed has three connections with the blood stream: the sinusoidal vessels, the veins, and the arteries (Fig. 1). Since the direction of flow in none of these vessels is determined by valves, we believe that it must be determined normally, and in any pathological condition met clinically by the pressures in the respective vessels, and by the obstruction to flow encountered. Our experiments support this view and indicate that in double coronary artery occlusion the flow is from the veins into the capillary bed. This irrigation by the venous system may be significant in other cardiac conditions.

The pain present in angina pectoris and in certain cases of localized coronary occlusion is usually regarded as due to an anoxemia of the

myocardium. This pain usually disappears with the inception of cardiac decompensation, with the onset of atrial fibrillation, or with the development of complete heart-block. Mackenzie²⁷ believes that shortness of breath so limits activity in these conditions that the patients are prevented from exerting themselves sufficiently to induce an attack of angina. This explanation has not been completely satisfactory (McCrae²⁶). If we accept the current belief of the anoxemic origin of the pain, then, on the basis of our experimental findings, we are in a position to offer another explanation for the disappearance under the conditions just noted. In cardiac decompensation and atrial fibrillation there is produced an increase in the intra-atrial pressure which favors a reversal of flow in the veins with its resulting irrigation of the capillaries of the anoxemic areas.

In complete heart-block, especially with the inception of Adams-Stokes syndrome, the pressure relations are again such as to favor a reversal of flow in the veins with the resulting irrigation of the myocardium. During the periods of asystole the coronary artery pressure falls to an extremely low level. We suggest that the continuance of atrial contractions during ventricular standstill are largely responsible for cardiac irrigation, as a result of which the vitality of the myocardium is so maintained, that a succeeding, effective impulse causes restoration of the idioventricular rhythm. Instances of recovery from ventricular fibrillation have been reported in man.¹⁷ In this condition irrigation of the ventricular muscle, by the coronary arteries is extremely unfavorable, but it could be easily attained by the reversal of flow in the heart veins.

SUMMARY

The myocardial capillary bed has three sets of connecting vessels. Named in the order of their embryological appearance and function these are: the sinusoidal vessels (in which are included the Thebesian Veins), the cardiac veins, and the coronary arteries. With the elimination of the arteries as in double coronary occlusion, the mode of irrigation of the capillaries has not been understood.

The direction of flow in the cardiac vessels joining the right heart was investigated under conditions simulating double coronary artery occlusion. Particles too large to pass through the lungs were injected into the veins, toward the heart, in anesthetized, heparinized dogs. These particles were uniformly found in the coronary sinus and the coronary veins. Their size was too great, and the arborizing and anastomosing veins were too small, to allow for any course of flow other than from right atrium to veins. The sinusoidal vessels (Thebesian veins) were excluded as a possible source of these particles in the veins, although irrigation of the capillaries in part, by them, was not excluded.

With a low pressure in the capillary bed (as in cases of double coronary occlusion or as in our experiments), flow in the veins during atrial systole is probably toward the capillary bed, the capillary bed being emptied during the ensuing ventricular systole. In arterial occlusion this would give a flow and ebb circulation for the myocardial capillaries by way of the veins.

This irrigation by venous channels may explain the disappearance of pain in angina pectoris, with the inception of those complications accompanied by a fall in the coronary artery pressure.

Most of the experiments for this study were carried out in the Department of Research Surgery. We thank Dr. I. S. Ravdin and his staff for the many facilities which they furnished us.

We are indebted to Dr. H. C. Bazett, Professor of Physiology, who reviewed our experiments.

REFERENCES

1. Abbott: In Blumer's Bedside Diagnosis, Philadelphia, 1928, Vol. II, p. 499, W. B. Saunders Company.
2. Abernathy: Phil. Trans. Roy. Soc., London (for 1798), 18: 287, 1809.
3. Bochdalek: Arch. f. Anat., 302, 1868.
4. Cabot and Mallory: New England J. Med., 202: 287, 1930.
5. Caldani and Caldani: Icones Anatomicae, III, 1810, Venetia.
6. Grant: Heart, 13: 261, 1926.
7. Grant and Regnier: Heart, 13: 286, 1926.
8. Grant and Viko: Heart, 15: 103, 1929.
9. Gross: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber.
10. von Haller: First Lines of Physiology, Cullen Translation, Vol. I, p. 75, Edinburgh, 1786.
11. Halpert: Heart, 15: 129, 1930.
12. Henle: Anatomie, Braunschweig, 1880, p. 245, Vieweg u. Sohn.
13. Hoyer: Arch. f. mikr. Anat., 13: 603, 1876.
14. Hyrtl: Lehrbuch der Anatomie, Wien, 1884, p. 999, Wilhelm Braumüller.
15. Jamin and Merkel: Die Koronararterien des Menschlichen Herzen in Stereoskopischen Röntgenbildern, Jena, 1907.
16. Kampmeier: AM. HEART J. 4: 210, 1928.
17. Kerr and Bender: Heart, 9: 269, 1922.
18. Krause: Handbuch der Menschlichen Anatomie, Hanover, 1879, Hahnsche Buchhandlung.
19. Kretz: Virchows Arch. f. path. Anat., 266: 647, 1927.
20. Krogh: The Anatomy and Physiology of Capillaries, New Haven, 1922, Yale University Press.
21. Lannelongue: Circulation veineuse des parois auriculaires du coeur, Thèse de Paris, 1867.
22. Leary and Wearn: AM. HEART J. 5: 412, 1930.
23. von Langer: Sitz. d. Kais. Akad. d. Wiss. Wien, 1880, 3 Abt., 82, 25.
24. Lancisius: de Motu Cordis, etc., Luguni Batavorum, 1740.
25. Lewis: Anat. Anz., 25: 261, 1904.
26. McCrae: Am. J. M. Sc., 179: 16, 1930.
27. MacKenzie: Angina Pectoris, London, 1923, Oxford University Press.
28. Mettier, Zschiesche, and Wearn: Tr. A. Am. Physicians, 44: 345, 1930.
29. Minot: Proc. Boston Soc. Nat. History, 29: 185, 1900.
30. Morgagni: De sedibus et causis morborum, etc., Lib. II, Venetia, 1761, Typographia Remondiniana.
31. Nussbaum: Arch. f. mikr. Anat., 80: 450, 1912.
32. Poirier, Charpy, et Nicolas: Traité d'Anatomie humaine, Paris, 1912, Tome II, Angéiologie.
33. Porter: Am. J. Phys., 1: 71, 1898.
34. Pratt: Am. J. Phys., 1: 92, 1898.

35. Pratt: Boston M. & S. J., 190: 8, 1924.
36. Richards: Am. J. M. Sc., 170: 781, 1925.
37. Senac: Traité de la structure du coeur, Paris, 1749.
38. Spalteholz: Anat. Anz., Ergänzungsheft zum 30: 141, 1907.
39. Spalteholz: Über das Durchsichtigmachen von menschlichen und tierischen Präparaten, Leipzig, 1911, S. Hirzel.
40. Spalteholz: Die Arterien der Herzwand, Leipzig, 1924, S. Hirzel.
41. Thebesius: Dissertatio de circulo sanguinis in corde, Lugduni Batavorum, 1708.
42. Verheyden: Anatomiae corporis humani, Coloniae, 1712, Chapter X, p. 180, Edmond Socios.
43. Vieussens: Nouvelles decouvertes sur le coeur, Toulouse, 1706.
44. Wearn: J. Exper. Med., 47: 293, 1928.
45. Winslow: Exposition anatomique de la structure du corps humaine, Paris, 1776, La Veuve Savoye.
46. Yater: Arch. Path., 7: 418, 1929.

POSTURAL HYPOTENSION

A CASE REPORT*

H. H. RIECKER, M.D., AND E. G. UPJOHN, M.D.,
ANN ARBOR, MICH.

POSTURAL hypotension was established as a clinical entity by Bradbury and Eggleston¹ in 1925 with a report of three cases. In 1928 two cases were reported by Ghrist and Brown² and two by W. T. Vaughan.³ The following case makes eight now reported, but it is probable that the syndrome is much more common than the reports indicate.

The clinical picture now is well established and permits recognition of the disease from the history. The essential points are the complaint of dizziness upon changing the position of the body from supine to erect and the prompt relief of the dizziness by reassuming a reclining posture. This may vary from slight vertigo to actual fainting. The diagnosis is confirmed by blood pressure readings in the two positions.

Certain other associated symptoms seem sufficiently common to be included in the symptom complex. These are a marked pallor of the face during the attack with temporary blurring of vision and involuntary closing of the eyes. The hands and feet become cyanotic during the erect posture. There are also numbness, tingling, and slight convulsive jerking of one of the arms, frequently associated with sweating of the limb. The jerking movement is not unlike that seen in the Stokes-Adams syndrome or carbon monoxide poisoning, and might be mistaken for an epileptiform seizure should fainting occur. Weakness, ease of fatigue, and dyspnea on exertion are common. It has been noted that patients feel more uncomfortable during the summer months.

In all cases it is agreed that the basis of symptoms is a relative anemia of the brain due to lowering of the cardiac output in the erect position. There is no agreement in the cases reported as to the pathological change affecting this occurrence.

CASE REPORT

A native married American, aged sixty years, laborer, complained of diarrhea and dizziness gradually increasing for two years. The colitis disappeared following the use of a high vitamin diet and iodine, but the dizziness persisted until the patient was obliged to lie in bed constantly. On arising to the standing posture he immediately noted dizziness and a coarse jerking of the left forearm. The

*From the Department of Internal Medicine of the the University of Michigan, Ann Arbor, Michigan.

symptoms were alleviated somewhat by walking rapidly, but reappeared promptly upon standing still. The patient easily became short of breath upon exertion. There had been no loss of appetite. Dizziness was more pronounced in the morning following a bowel movement. While sitting quietly in a chair the patient often noticed increased sweating of the left side of the body.

Physical Examination.—Height 70 inches, weight 180 pounds. Sthenic habitus with rather wide costal angle, appearance and age coinciding. The patient was hyposensitive according to Libman's classification. Moderate emphysema. The vital capacity was 2300 c.c. or 55 per cent of the normal. The cardiac silhouette was of the aortic type but not definitely abnormal. There was general arterio-

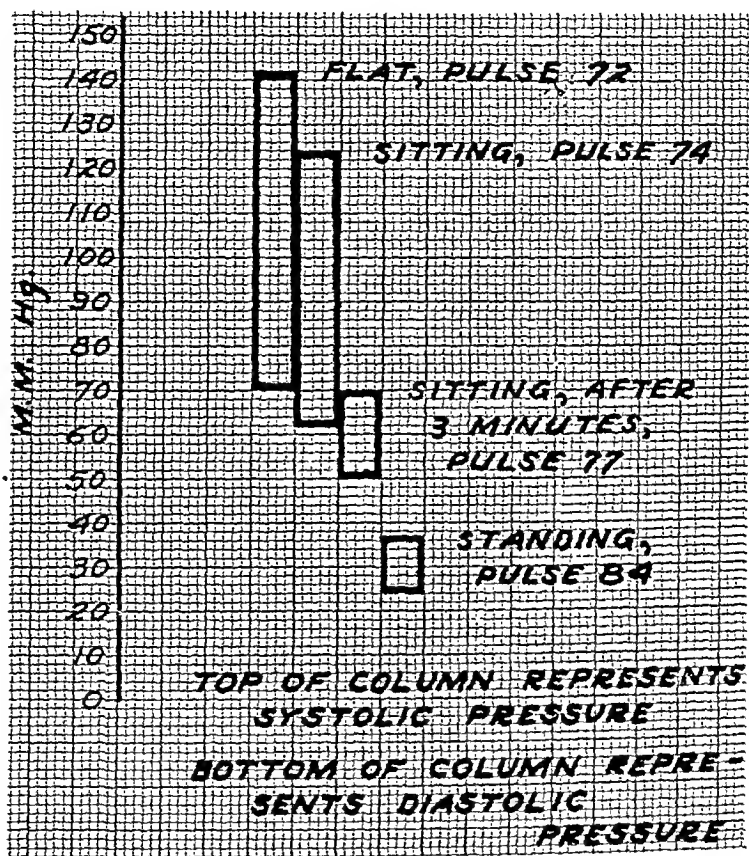


Chart 1.—Pulse pressures in the several positions.

sclerosis, and the retinal arteries showed moderate sclerosis. Blood pressure readings: right arm: supine 140/70 mm., sitting 70/50, standing 38/25, right leg (above knee): supine 235/70, sitting 212/80, standing 145/76.

Laboratory Data.—Urine negative. Peripheral blood normal. Electrocardiogram normal. X-ray studies of chest, gastrointestinal tract and skull negative. Labyrinthine tests normal. Basal metabolic rate -1 per cent (test satisfactory).

The following special examinations were directed toward the complaint: 0.3 c.c. adrenalin subcutaneously produced an increase in blood pressure to 200/120 mm. This was accompanied by a large number of extrasystoles and a sharp constrictive substernal pain. The patient became extremely sick and required the immediate application of amyl nitrite for relief, suggesting latent angina pectoris (Levine). However, dizziness could not be induced while the effect of adrenalin remained.

Phenolsulphonephthalein Tests.—Supine excretion in two hours (intravenously) 35 per cent, sitting 11 per cent. In one case of Ghrist and Brown the phenol-sulphonephthalein output was greater in the standing position. Blood pressure readings were taken by means of the Tycoos recording sphygmomanometer in the various positions. In the erect posture besides the extremely low blood pressure the pulse pressure diminished to about 10-15 mm. mercury. When the patient was placed at rest with the head down, the blood pressure rose from 140/70 to 170/90 showing that the vasomotor center was unable to maintain the normal pressure in this position as well.

Studies on the heart were directed to show alterations in size with position by teleroentgenogram. No difference beyond the limits of normal could be demonstrated.

The water excretion test of Volhard was done in the two positions as a further study of the kidney circulation. In the supine position the output in four hours

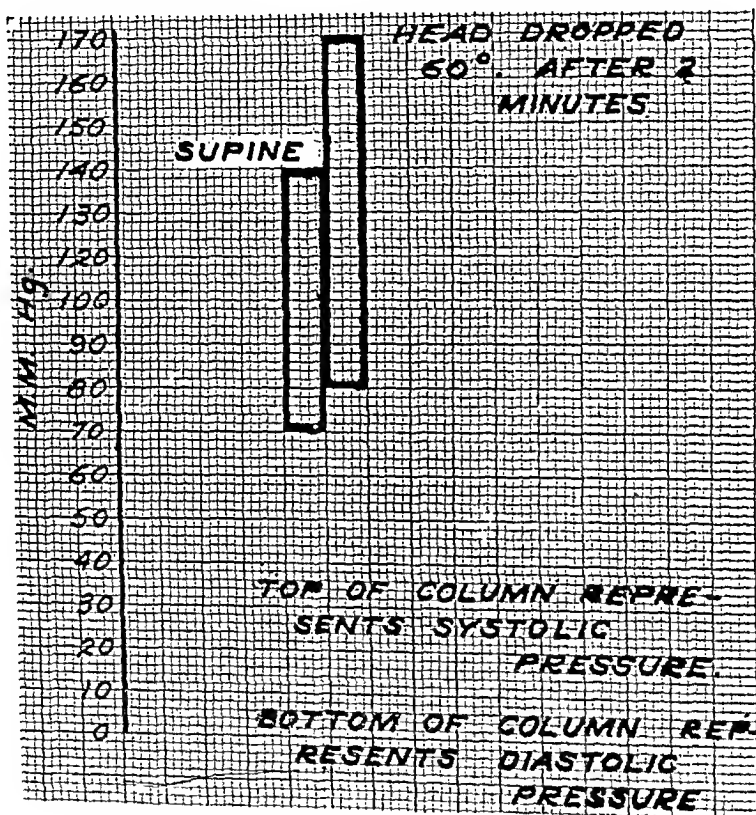


Chart 2.—Change in pulse pressure with head down.

was 1200 c.c. from an intake of 1500. In the standing posture it was 510 c.c. This test demonstrates (1) normal kidney function; (2) a deficient kidney circulation in the upright position; and (3) confirms the findings with the phenolsulphonephthalein tests.

The capillary blood pressures were done in the two positions using the finger tips. Pressure readings of 13 cm. of water were obtained in both positions constantly, by a trained observer. It was noted clinically that when the patient was standing the feet became cyanotic and that this subsided while the patient was walking.

Treatment with small doses of ephedrine (50 mg. twice a day) following the suggestion of Ghrist and Brown seemed only moderately successful, and with this the patient left the hospital, after one month's observation, not able to resume his occupation. The changes in blood pressure are shown graphically in Charts 1, 2, and 3.

COMMENT

This case is somewhat different from those reported by Bradbury and Eggleston in that there was no evidence of a thymolymphatic constitution. The blood pressure readings and the pulse pressures were lower in the reclining posture than in any of the seven cases previously reported.

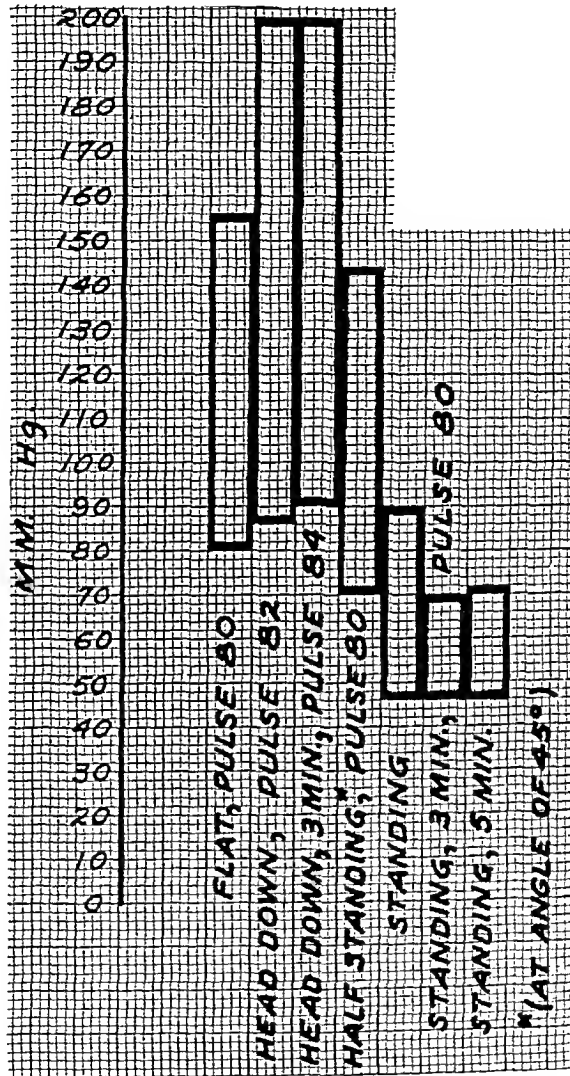


Chart 3.—Changes after use of 100 mg. of ephedrine (patient on table).

We can find no explanation of the underlying pathology in this case other than that the vasomotor regulating mechanism was incapable of responding in a normal manner to changes in position. This is shown by the fact that it failed to respond when the head was down as well as when the standing posture was assumed. It is suggested that the pathological lesion here might be that of cerebral arteriosclerosis with a special predilection to vasomotor mechanism. The experiments of Leonard Hill in 1887 explaining the changes in blood pressure with

posture on the basis of bleeding into the splanchnic area are difficult to confirm, and we are quite loath to accept these results as applying to this case or to the others in the literature, although a marked hydrostatic effect cannot be denied. There was no evidence of congestion of the kidneys on standing (casts, red cells and high water excretion) nor in any of the eight cases did increased abdominal pressure by bandage change the blood pressure. With the cyanosis of hands and feet, the marked decrease in kidney function, and the negative effect of abdominal bandage, it is obvious that there is a general rather than a splanchnic dilatation of the blood vessels in the erect posture.

That the peripheral vasomotor endings are intact is shown by the response to epinephrine and ephedrine.

CONCLUSIONS

A case of postural hypotension in an elderly man is reported in which arteriosclerosis and a lowered vital capacity were prominent findings.

The pathological physiology in this case seems to be a greatly reduced stroke volume of the heart induced by failure of the vasomotor nervous center to respond to the hydrostatic effect of the standing posture.

With the report of eight cases the clinical syndrome is well defined, and capable of recognition from the history.

REFERENCES

1. Bradbury, S., and Eggleston, Cary: Postural Hypotension, *AM. HEART J.*, 1: 73, 1926; and 3: 105, 1928.
2. Ghrist, D. G., and Brown, G. E.: Postural Hypotension with Syncope; Its Successful Treatment with Ephedrine, *Am. J. M. Sc.*, 175: 336, 1928.
3. Vaughan, W. T.: Clinical Study of Low Blood Pressure, *Virginia M. Monthly*, 54: 757, 1928.

CARDIAC ANOMALY (SO-CALLED DOUBLE LEFT AURICLE)

REPORT OF A CASE*

GEORGE A. PALMER, M.D.,
CLEVELAND, OHIO

INTRODUCTION

THE heart is subject to more individual variations and anomalies than any organ in the body. The majority of these anomalies can be explained on an embryological basis. However, there are a few cases for which no adequate explanation has yet been offered. This case falls under the latter category. Cardiac anomalies can be divided into (1) viable and (2) nonviable. Many cardiac anomalies are not recognized until death, while others are recognized accidentally, and still others act as a primary factor in the cause of death early in life. There are innumerable classifications of cardiac anomalies, both clinical and pathological, but that of viable and nonviable seems best suited to this discussion.

CASE REPORT

History.—The patient, L. P., a male infant of three and one-half months, was brought to the University Hospital with a chief complaint of “trouble with the thymus gland.”

Family History.—The mother and father were living and well. There were six other children, living and well; none were dead. There had been two miscarriages, one preceding the birth of normal children, the other following the birth of normal children. There had been no stillbirths.

Birth and Developmental History.—The child was born at full term; the delivery was normal and spontaneous. He was quite blue at birth. He weighed eleven pounds. There were no convulsions following delivery.

Present Illness.—The mother stated that the child had always been rather sickly, that he had diarrhea during the first five weeks of his life and had had intermittent attacks of difficulty in breathing, associated with cough and cyanosis. These attacks increased in frequency and severity as time went on. When the infant was five weeks old, the mother noticed a change in his voice. Previously it was normal in quality, whereas it changed to a high-pitched reedy note, suggestive of some obstruction in the larynx. At the onset, the cyanosis was noted only about the lips and nail-beds, only during the attacks of difficulty in breathing. As time went on, however, the child became constantly cyanotic. Two roentgen-ray treatments were given over the region of the thymus before the child was admitted to this hospital.

Course in the Hospital.—The child was put in semi-Fowler's position, given oxygen almost constantly for cyanosis, codein for restlessness and 3 minims of digifoline every three hours. A loud systolic murmur was heard at the apex and

*From the Department of Pathology, University Hospital, Ann Arbor, Michigan.

transmitted practically throughout the chest. Anteroposterior and lateral plates of the chest were taken which showed marked enlargement of the heart, incomplete aeration of the upper lobe on each side and slight tracheal contraction in the lateral projection, probably due to anteroposterior enlargement of the thymus. Examination of the blood showed R.B.C. 5,100,000, W.B.C. 12,900, hemoglobin 82 per cent. The urine examination on entrance was negative. The day following admission the child's temperature was 104 degrees F., and râles were heard over the left chest and axillary region. The child's condition became progressively worse. The temperature rose steadily and finally reached 108 degrees F. The respirations ceased forty-eight hours after admission. A clinical diagnosis of congenital heart disease with questionable bronchopneumonia was made.

Autopsy Findings.—An autopsy was done one and a half hours after death. The body, 60 cm. in length, appeared to be somewhat younger than the stated age. It was considerably undernourished and underweight. The lips and nail-beds showed a marked degree of cyanosis. There were no other external findings of significance.



Fig. 1.—Shows the exterior of the heart. The anterior surface is made up entirely of right ventricle and auricle.

The autopsy was limited to the thorax only, but examination of the abdominal viscera while in situ revealed no abnormalities. The lower border of the liver measured 8 cm. below the ensiform cartilage and 5 cm. below the right costal margin. The diaphragm was beneath the sixth rib on the left and the fifth interspace on the right.

On removing the sternum, the enlarged heart was found to occupy a large portion of the thoracic cavity. Both lungs were compressed to the lateral thoracic wall, the left more so than the right. The thymus gland, occupying a small part of the anterior mediastinum, was normal in size.

The heart itself was markedly distended with blood. It lay almost transversely in the thoracic cavity. Fig. 1 shows the exterior of the heart as it lay in the mediastinum, with the anterior surface made up entirely of right ventricle and auricle. The heart was not measured while it was in the body, but after it was removed and had bled out, it measured $8 \times 6 \times 5.5$ cm. The apex was formed entirely by the right ventricle. The subepicardial fat was slightly decreased in amount. The musculature had the normal red color. There were no gross areas of fibrosis.

On opening the left side of the heart the ventricle was found to be very small. The wall averaged only 4 mm. in thickness. The inside diameter of the left ventricle measured only 1.5×2 cm. There were no interventricular openings. On opening the

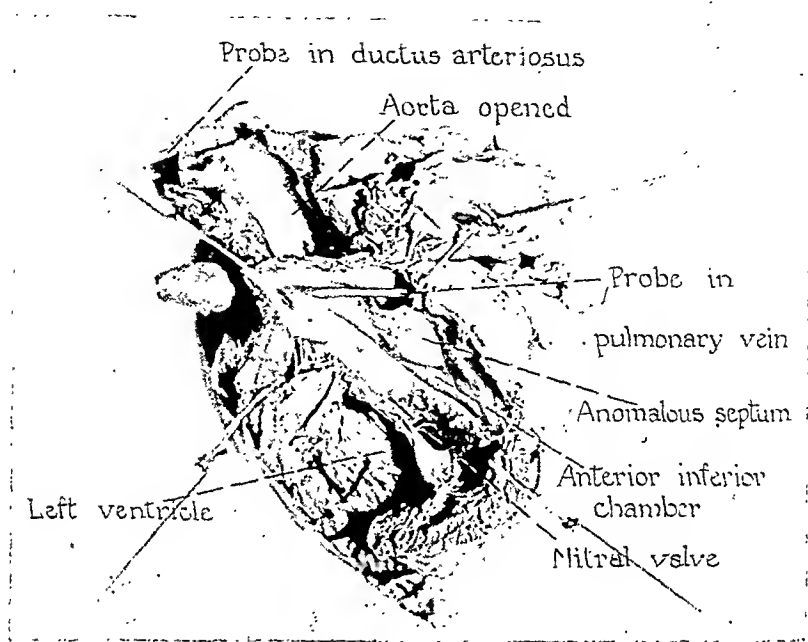


Fig. 2.—Shows the left heart opened. The probe is in the pulmonary vein and extends into the anteroinferior chamber of the left auricle. (The intraauricular opening has been stretched, causing it to appear much larger than it actually was.)

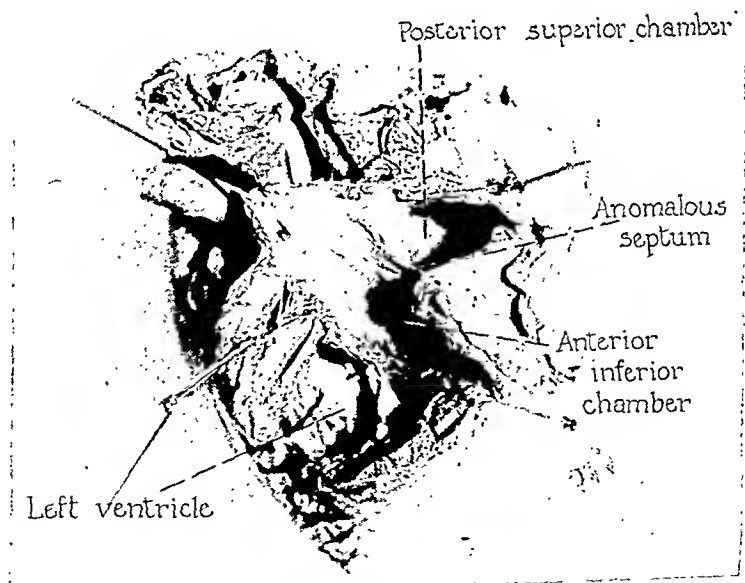


Fig. 3.—Same as Fig. 2 except that the anomalous septum has been put on the stretch, thereby showing the posterosuperior and anteroinferior chambers of the left auricle.

left auricle the mitral valve was found to be normal. Arising, however, from the posterolateral surface of the left auricle and extending toward the interauricular septum was an anomalous fibromuscular septum. This septum almost completely divided the left auricle into a larger posterosuperior, and a smaller anteroinferior

chamber, the inside diameters being 1.5×2.5 cm. and 1×1.5 cm. respectively. The septum measured $11 \times 11 \times 1$ mm. Its free margin was adjacent to the interauricular septum, there being approximately only a 6 mm. slit for the blood to pass the septum (Fig. 2). The miniature auricular appendage was given off the anteroinferior chamber. Fig. 3 shows the left anriele and ventriele opened with anomalous septum.

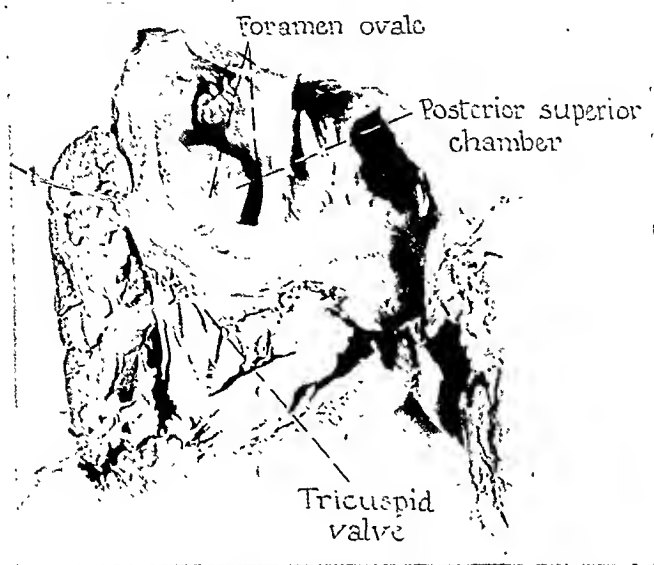


Fig. 4.—Interior of right heart showing the large foramen ovale and fusion of tricuspid valve. Note thickness of right ventricular wall.

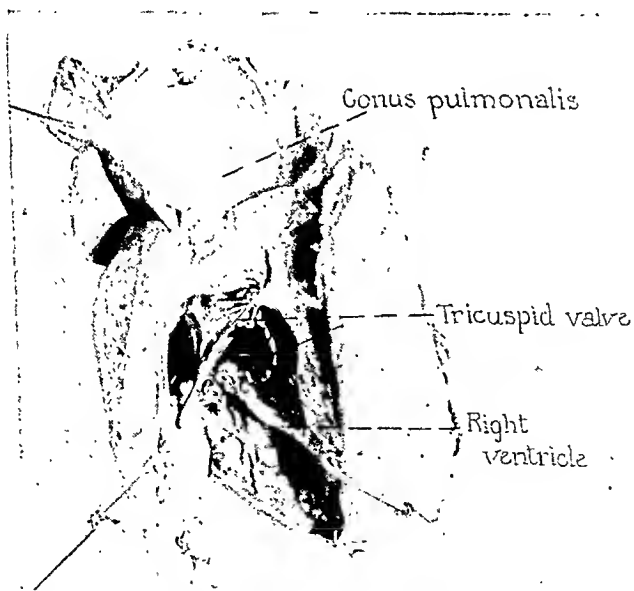


Fig. 5.—This picture shows the much dilated conus pulmonalis. (Compare with Fig. 2 which shows the aorta opened.)

The pulmonary veins had united and entered the posterosuperior chamber by a single vein. The much enlarged foramen ovale, measuring 1×2 cm., was located almost opposite the entrance of the pulmonary vein in the interauricular septum, thereby connecting the right auricle and the posterosuperior chamber.

The inside diameter of the right auricle measured 2.3×3 cm. Two of the cusps of the tricuspid valve were fused to produce in reality a bicuspid valve. The wall of the right ventricle averaged 8 mm. in thickness. The inside diameter of the cavity measured 4.3×4.5 cm. (Fig. 4.)

The pulmonary artery was considerably larger than the aorta, measuring 12 mm. in diameter, as compared with the aorta which measured 7.5 mm. in diameter (Fig. 5). The ductus arteriosus was patent, the lumen measuring 1.5 mm. in diameter. Although patent, it was evident that only a very small amount of blood was transmitted through it. The coronary vessels were normal in their distribution.

Microscopic Examination.—The aorta showed a patchy slight sclerosis of the intima. The cardiac musculature was well formed but rather hypertrophic for the age. The lungs showed partial atelectasis, congestion and small petechial hemorrhages. All of the vessels were dilated and their walls showed slight hypertrophy, particularly the arterics. There was no pneumonia. The peribronchial lymph nodes were rather hyperplastic. Both the larynx and esophagus were negative. The thymus showed fibroid rather than fatty atrophy. All adipose tissue showed starvation atrophy.

LITERATURE

There have been to date ten fully reported cases of this extremely interesting condition. The first case to be reported was by Church in 1868. Fowler in 1882 reported a case in which the patient lived forty-two years. He described a vertical membrane with many perforations. The presence of these perforations may be the significant factor in the relatively long length of life. Griffith reported two cases, the first in February, 1896, to the Anatomical Society, describing an upper and lower left auricle. The second, in 1903, was found in a man forty-three years old who died of Bright's disease. Sidney Martin in 1899 reported a case with upper and lower left auricle. Peter Potter and Ranson in 1904 reported a case found in a colored child who died of asphyxia. They described three right and two left pulmonary veins emptying into the upper posterior auricle. There were five small openings and one large opening in the anomalous septum. This case would tend to show that the presence of perforations in the septum is not a factor in determining the length of life. Borst reported a case found in a man thirty-eight years old. He described one left and four right pulmonary veins emptying into the upper posterior chamber. The foramen ovale was not patent. William and Abrikossoff, in 1906, reported a case found in an eleven-year-old boy. The left auricle was divided into two parts; the upper surface of the septum was concave, the lower convex. In the anteromedial part of the septum was a one-half centimeter opening. Peter Hosch in 1907 reported a case found in a twenty-five-day-old infant. There was a wide open ductus Botalli. Just posterior to the foramen ovale was another interauricular opening. Stoeber in 1908 reported a case with no opening in the anomalous septum of the left auricle. The veins of both upper lung lobes emptied into the right auricle, so only the veins of the lower lobes emptied into the upper small left auricle. The middle lobe of the right

lung was absent. There was a patent foramen ovale with a rudimentary valve, which was a continuation of the septum itself.

SUMMARY

There is no adequate embryological explanation for this anomalous septum in the left auricle, as there are no embryological rests from which it could develop. A plausible but not proved explanation is that the anomalous septum is an inversion or direct extension of the wall of the pulmonary vein, i.e., that in reality the smaller antero-inferior chamber is the normal left auricle, while the posterosuperior chamber is the dilated end of the pulmonary vein. Another possible explanation, although not applicable to this particular case, is that the anomalous septum may have arisen on the basis of (1) a fetal endocarditis or (2) an organization of thrombi.

This case had both a peripheral and aortic anoxemia. There was insufficient blood pumped from the left ventricle through the aorta to the peripheral circulation, and also this blood was mixed blood. The blood in the pulmonary circulation was sufficiently aerated, but the difficulty was that an insufficient amount of this blood reached the systemic circulation.

There are three factors which determine the duration of life in cases of this type: (1) the degree which the intraauricular septum prevents the blood from the pulmonary veins from passing through the mitral valve; (2) the size of the foramen ovale; (3) the relation of the intraauricular septum to the pulmonary veins and the foramen ovale.

The large foramen ovale was the only factor in this case which was conducive to long life. The fact that the anomalous septum so nearly completely divided the left auricle and thereby prevented the blood entering from the single pulmonary vein from passing the mitral valve to the left ventricle was a highly important factor in the short duration of life. Perhaps the most important factor, however, was the relation of the anomalous septum to the pulmonary veins and foramen ovale. The intraauricular septum in this case was very considerably stronger than the interauricular septum, and there was only a 6 mm. slit for the blood to pass the septum to reach the mitral valve and thus the left ventricle. The large foramen ovale was located almost opposite the entrance of the single pulmonary vein, thus making a much freer communication between the posterosuperior chamber of the left auricle with the right auricle, than with the antero-inferior chamber. These factors make it clear that the infant died a cardiac death with both an aortic and peripheral anoxemia.

REFERENCES

1. Church, W. S.: Congenital Malformation of Heart; Abnormal Septum in Left Auricle, *Tr. Path. Soc., Lond.*, 19: 188, 1868.
2. Fowler, J. K.: Membranous Band in the Left Auricle, *Tr. Path. Soc. Lond.*, 33: 77, 1881-2.

3. Griffith, W.: Note on a Second Example of Division of the Cavity of the Left Auricle into Two Compartments by a Fibrous Band, *J. Anat. Physiol.*, 37: 255, 1902-1903.
4. Martin, Sidney: Anatomical Society, Cambridge, 1899.
5. Potter, Peter, and Ranson, S. Walter: A Heart Presenting a Septum Across the Left Auricle, *J. Anat. Physiol.*, 39: 69, 1904.
6. Borst: Ein Cor triatriatum, *Verhandl. d. deutsch. path. Gesellsch.*, 9: 178-192, 1905, 1906.
7. William, N., and Abrikossoff, A.: Ein Herz mit linkem Doppelvorhof, *Virchows Arch. f. path. Anat.*, 203: 404, 1911.
8. Hosch, Peter Hans: Zur Lehre der Missbildungen des linken Vorhofs. I. Ein Sehnenfaden im linken Vorhof. II. Ein Herz mit linkem Doppelvorhof, *Frankfurt. Ztschr. f. Path.*, 1: 563, 1907.
9. Stoeber: Ein weiterer Fall von Cor triatriatum mit eigenartig gekreuzter Mündung der Lungenvenen, *Virchows Arch. f. path. Anat.* 3: 252, 1908.

A QUALITATIVE COMPARISON OF VARIOUS DIGITALIS BODIES*

HARRY GOLD, M.D., WILLIAM HITZIG, M.D., BEN GELFAND, M.D.
AND HERMAN GLASSMAN, M.D.
NEW YORK, N. Y.

TWO facts concerning the action of digitalis made possible the present investigation: (1) that digitalis acts upon a number of cardiac structures and produces a number of effects that can be detected in the electrocardiogram—sinus slowing, depression of conduction, increased rhythmicity of the A-V node or ventricle action upon the ventricle to change the T-wave or the R-T (or S-T) interval; and (2) that it requires more of the drug to produce some of these effects than others. This study was planned to ascertain whether or not the percentages of the fatal doses that produce the various changes are the same for different members of the digitalis group.

It is well known that digitalis leaves themselves, the pure glucosides and the various other members of the group, show wide differences in their chemical composition, physical properties, and pharmacological behavior (potency, rate of absorption, persistence of action, rapidity of onset of action). There have been no satisfactory studies of the question of qualitative differences in the cardiac action of different digitalis bodies. Our use of the term, qualitative differences, may be best explained by the following illustration. Apomorphine may be prepared from morphine by the removal of a molecule of water, and each drug possesses most of the actions of the other, but the ratios of the intensity of action upon one structure to that upon another have been so markedly altered that in effect it amounts to a qualitative change in the actions of the drugs, so that one is used to stimulate the vomiting center and the other to depress the centers for the perception of pain. With reference to the digitalis bodies there was the question whether the chemical differences that render one less soluble in water, more readily absorbed from the gastrointestinal tract, more persistent in its action, may not also change the relative intensity of the different cardiac actions so that whereas, for example, ectopic beats with one specimen might be called forth only after 50 per cent of the fatal dose, these might be produced with another specimen after as little as 20 per cent of the fatal dose. Such differences would of course be qualitative in effect, because under such conditions, two specimens might be equally potent when measured in terms of the

*From the Department of Pharmacology, Cornell University Medical College, New York.

fatal action, yet one might be effective in slowing the sinus rate while the other would not, since in the latter case ectopic beats would appear before sufficient drug was present to slow the sinus. As a matter of fact, the results obtained by the usual methods of bio-assay of digitalis have been criticized on the ground that, although they furnish an estimate of the relative toxic activity of different specimens, we have not sufficient knowledge as to what extent these variations in toxic activity reflect the relative potency of different specimens with reference to phenomena occurring within the therapeutic range.

It was, therefore, an important question to determine, not only whether different members of the digitalis group produce the same types of cardiac changes, but whether the ratios of the amounts of the drug required to produce these changes to the amounts of the drug required to cause death are constant or vary for different digitalis bodies. This was made the subject of the present study. These data would afford an indication as to whether or not different digitalis bodies act with the same relative intensity (in relation to the fatal dose of that preparation) upon the different structures of the heart.

EXPERIMENTAL PROCEDURE

Seventy-seven experiments were carried out with six members of the digitalis group showing marked differences in their physical chemical and pharmacological properties:

1. A tincture of digitalis of an American grown leaf (of high potency).
2. A tincture of digitalis of a German grown leaf (of low potency).
3. A specimen of the chloroform fraction, "purified tincture" of digitalis (well absorbed, very persistent in action).
4. A tincture of adonis (poorly absorbed, very persistent in action).
5. Ouabain (soluble in water, poorly absorbed, relatively brief persistence of action).
6. Digitoxin (Merek) (insoluble in water, well absorbed, very persistent in action).

The tinctures were diluted with 19 volumes of normal saline after the alcohol had been evaporated with moderate heat. A few of the experiments were carried out without the removal of the alcohol, but the results were essentially the same. The ouabain was dissolved in normal saline so as to make a solution of one in 100,000. The digitoxin was made into a one per cent alcoholic solution, and the latter was diluted with normal saline so as to make a solution of digitoxin of one in 10,000. About 5 per cent of the average fatal dose of the drug was injected from a burette at intervals of approximately five minutes until death. Cats were used in all. The animal was kept tied in the supine position throughout the experiment. Several electrocardiograms (only Lead II was used) at intervals of from five to fifteen minutes were taken before the injection of the drug was started. A tracing was then taken just before each injection. The movement of the string was sometimes observed throughout the experiment, and additional tracings were taken when abnormalities were detected. For each experiment there were approximately twenty-five separate tracings representing about 40 feet of electrocardiogram for analysis. Eleven to sixteen animals were used in the study of each preparation.

Anesthesia.—It was obviously desirable to carry out these experiments with the animals in a condition as nearly normal and constant as possible. It has been shown that ether anesthesia depresses the vagus and diminishes its response to stimulation by morphine.² Since some of the digitalis effects depend upon vagal influence, it seemed possible that the order of some of the changes resulting from the drug might be altered by the ether anesthesia. Furthermore, it appeared that a fixed anesthetic might in several ways prove more satisfactory. The effects of anesthesia by the intravenous injection of barbital sodium was tested in four animals. Each of three of these received 200 milligrams per kilogram in a single dose. When some anesthesia had been induced, the injection of digitalis was carried out in the usual manner. The results were very variable, and while it cannot be stated whether larger numbers of experiments would not reveal a tendency different from that in unanesthetized animals, the behavior toward digitalis of each of these three is duplicated essentially in the unanesthetized group (see animals 14, 15, 16 of Table II). Electrocardiograms were taken approximately every fifteen minutes for several control records before the barbital, then after the barbital injections for periods of 165 minutes (in one experiment in which only barbital was used), 272 minutes (animal 14 of Table II), 233 minutes (animal 15 of Table II), and 141 minutes (animal 16 of Table II). In the first animal the heart rate varied between 140 and 160 a minute during forty minutes of control. During the first ten minutes following the injection of 150 milligrams per kilogram there was almost incessant struggling. An additional 100 milligrams per kilogram were injected, and after about twenty minutes the animal became quiet. The heart rate, however, was accelerated to 220 a minute which rate gradually diminished during the next two hours to 180 a minute. The mean blood pressure (taken with the mercury manometer from the carotid artery) had fallen from 180 to 126 mm. The form of the electrocardiographic deflections showed no significant changes. The temperature fell to 99.4 degrees F. and the animal began to shiver. The condition of the animal was, therefore, not constant for any considerable period after the injection. In experiment 14 (Table II) the heart rate diminished gradually from 225 to 150 during a period of two and one-half hours, and the blood pressure fell from 160 to 100 mm. In experiment 15 (Table II) the rate at first increased from 210 to 255 a minute, then gradually diminished during a period of about four hours to 185 a minute with reduction of the blood pressure during this time to 98 mm. The heart rate, however, continued to fall during the digitalis injection, and it was not possible to ascertain whether that was due to the digitalis or merely a continuation of the barbital action. In experiment 16 (Table II) the heart rate remained practically constant, though the animal continued to be restless throughout the experiment. The use of the fixed anesthetic was discontinued because the reaction to the barbital varied greatly; there was considerable restlessness even after very large doses, and there were progressive changes in the heart rate and blood pressure as well as in the general condition of the animal which occurred gradually over long periods of time.

The operation for the insertion of the cannula into the saphenous vein was performed during local anesthesia with phenol in oil, and the injections were made without any general anesthesia. Occasionally a cat tied down on its back lies there very quietly, but often there is repeated struggling resulting in wide fluctuations in the heart rate, and sometimes changes in the electrical axis of the heart altering the direction of the deflections, such as inversion of the T-wave, or change of an R to an S-wave. These changes were usually temporary and disappeared in subsequent tracings. We also found that ectopic beats were produced by struggling after doses of digitalis which were insufficient to produce them when the animal was quiet. Such response would be expected in view of the fact that some of the changes produced by digitalis depended upon the activity of the extracardial nerves,

and the changes will appear with smaller or larger doses depending upon whether struggling has intensified or diminished the activity of these nerves. This has been made the subject of a separate investigation. In dispensing with the anesthesia we have obviated the necessity of considering possible disturbing factors of another drug. It is well to note, however, that the condition of the unanesthetized animal is not normal in the strict sense and far from constant; the results obtained with digitalis in the animal whose ventricle is subjected to strong accelerator stimuli (as in violent struggle) are not the same in some respects as those obtained when the latter stimuli are absent. The data obtained under the conditions of these experiments, however, serve sufficiently to compare the behavior of different members of this group of drugs.

Electrocardiographic Criteria.—The effect of the drugs upon the sinus rate has not been considered in the interpretation of the results. With each of the specimens there were some instances in which the heart rate was greatly slowed during the injections. It was not possible, however, to ascertain the doses producing the first changes because of the marked fluctuations of the rates in the controls. The percentage of the fatal dose which produced the greatest slowing is indicated in the tables; in some instances no percentage is given (dashes in the tables) because while the slowest rate during the injection was actually slower than that during the control, the fluctuations were so wide that it was deemed unsafe to assume that the slowing was due to the drug.

The P-R intervals were determined by taking an average of about ten readings in each tracing (from beginning of P to beginning of Q or R). The change in conduction was relatively fixed for successive beats in most tracings; occasionally, however, it was of the type in which successive beats showed progressively increasing P-R intervals until dropped beats occurred (for example, animal 10 of Table VI). It is probable that the prolonged conduction in most instances was due to direct depression of the conducting system rather than to vagal influence or as the result of sinus slowing, because the vagus tone in most instances was very low as seen from the rapid heart rates, the first changes in conduction frequently occurred without any change in the sinus rate, and because when a change in conduction occurred it was usually persistent and not abolished by struggling which inhibited the vagus. The prolongation of conduction from tracing to tracing often occurred with almost imperceptible gradations; hence it was difficult to ascertain the first change. Since the average of several intervals in each of several control tracings usually showed variations in conduction time of less than 0.05 second, a tracing was regarded as showing a prolonged P-R interval only when a change of 0.05 second or more was present.

The changes produced in the T-wave and the R-T (S-T) segment were extremely variable. The form of the changes varied with the

form of the control deflections. The most constant feature was that a positive deflection became isoelectric, and then negative. The form of the R-T segment (or S-T segment when the S-wave was present) was found to be much more constant than the T-wave and therefore more satisfactory to follow as an index of digitalis action. The T-wave was extremely variable showing forms that were isoelectric, high, low, and occasionally negative in successive tracings of the control period, or even in the same tracing. Illustrations of the different types of changes in the T-wave, R-T and S-T segments will be published in another communication. As was the case with the P-R intervals, the changes sometimes occurred very gradually and with the marked variations in the controls; it was difficult to determine with precision in which tracings the first changes due to the drug had occurred. In the tables we refer to the dose of the drug producing the first change in the RT-T period. In some instances this represents the first definite change in the T-wave, in some, that of the R-T (S-T) segment, and in others, it represents a simultaneous change in both, depending upon which showed the first unmistakable deviation from the control tracings.

The ectopic beats were of either nodal or ventricular origin. At times they appeared as isolated beats or a bigeminal rhythm (every other beat a ventricular premature contraction); they often appeared for the first time as a ventricular tachycardia. In some animals ectopic beats occurred in one tracing, then were absent in the next two or three tracings even though additional doses of the drug had been injected. The early appearance of ectopic beats was often due to struggling, a phenomenon to which we have already referred. In three animals of the series ventricular ectopic beats appeared after a struggle before the injection of the drug was started. Even though these animals were apparently susceptible to spontaneous ectopic beats, they required practically the same dose of the drug to induce them as did normal animals. This is in harmony with the observation that patients susceptible to spontaneous premature contractions do not necessarily show any special susceptibility to their production by the digitalis bodies.³

Ventricular fibrillation was the cause of death in every animal used in this study.

RESULTS

The detailed analyses of the electrocardiograms are tabulated in the Tables I to VI. They show the extent of some of the changes as well as the doses required to produce them. These data are necessary to convey the proper appreciation of the extreme variability in the behavior of different animals to the *same preparation*. For example, animals 2 and 4 (Table II) required the same fatal dose, but in the first the only electrocardiographic change was an ectopic rhythm after

TABLE I
TINCTURE DIGITALIS (AMERICAN LEAF)*

| NO. | WEIGHT OF ANIMAL | FATAL DOSE | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | FIRST IN- CREASED P-R | LONGEST P-R IN PERIOD OF INJEC- TION | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | LONGEST P-R | SLOWEST SINUS RATE | ECTOPIC BEATS | | | | | |
|-----|------------------------|---------------|--------------------|---------------|------------------------------|-----------------------------|--|-------------------------------------|------|--------------------|-----------------------|----------------|--------------------------|--------------------------|-----------------------|-----------------------|-----------------------|--------------------|-----------------------|
| | | | C.C. PER KG. | IN CONTROL | | | | IN PERIOD OF INJEC- TION | SEC. | CHANGE IN RT-T | | | | FIRST IN- CREASED P-R | | % OF FATAL DOSE | % OF FATAL DOSE | C.C. PER KG. | % OF FATAL DOSE |
| | | | | | | | | | | C.C. PER KG. | % OF FATAL DOSE | | | C.C. PER KG. | % OF FATAL DOSE | | | | |
| 1 | 2.60 | 0.26 | 280 | 260 | 0.070 | --- | --- | 0.10 | 37 | --- | --- | --- | --- | 0.19 | 75 | | | | |
| 2 | 2.74 | 0.31 | 180 | 205 | 0.090 | 0.11 | --- | --- | --- | --- | 0.15 | 49 | --- | 0.18 | 57 | | | | |
| 3 | 2.60 | 0.33 | 220 | 210 | 0.080 | --- | --- | 0.10 | 30 | --- | --- | --- | --- | 0.16 | 50 | | | | |
| 4 | 2.22 | 0.34 | 210 | 220 | 0.070 | 0.080 | 0.100 | 0.09 | 27 | 0.16 | 47 | --- | --- | 0.18 | 53 | | | | |
| 5 | 2.30 | 0.35 | 200 | 160 | 0.078 | 0.085 | --- | 0.10 | 30 | 0.10 | 30 | --- | --- | 0.10 | 30 | | | | |
| 6 | 2.92 | 0.36 | 175 | 180 | 0.070 | 0.080 | --- | 0.12 | 33 | 0.22 | 60 | --- | --- | 0.14 | 40 | | | | |
| 7 | 2.24 | 0.38 | 225 | 160 | 0.075 | 0.085 | 0.120 | 0.09 | 24 | 0.11 | 30 | --- | --- | 0.13 | 35 | | | | |
| 8 | 2.40 | 0.44 | 220 | 135 | 0.070 | 0.080 | 0.095 | 0.13 | 29 | 0.31 | 71 | 76 | 71 | 0.27 | 61 | | | | |
| 9 | 2.50 | 0.45 | 210 | 180 | 0.070 | 0.080 | --- | 0.13 | 29 | 0.26 | 57 | --- | --- | 0.16 | 36 | | | | |
| 10 | 2.62 | 0.46 | 305 | 250 | 0.070 | 0.075 | --- | 0.14 | 30 | 0.18 | 40 | --- | --- | 0.21 | 45 | | | | |
| 11 | 3.30 | 0.56 | 220 | 190 | 0.060 | 0.080 | 0.100 | 0.15 | 27 | 0.27 | 49 | 57 | --- | 0.24 | 42 | | | | |
| 12 | 2.00 | 0.56 | 165 | 95 | 0.080 | 0.080 | 0.12-0.16 | --- | --- | --- | 0.21 | 38 | 56 | 0.31 | 56 | | | | |

*From evidence subsequently obtained.

*From evidence subsequently obtained it appears that the leaf was not as active as indicated by these figures but that the preparation was probably more than a 10 per cent tincture.

TABLE II
TINCTURE DIGITALIS (GERMAN LEAF)

| NO. | WEIGHT OF ANIMAL | FATAL DOSE | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | FIRST IN- CREASED P-R | LONGEST P-R IN INJEC- TION | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | LONGEST P-R | SLOWEST SINUS RATE | ECTOPIC BEATS | | |
|-----|------------------------|---------------|--------------------|---------------|------------------------------|-----------------------------|-------------------------------------|-------------------------------------|-------------------|-----------------------|--------------------------|----------------|--------------------------|-------------------|-----------------------|-----------------------|
| | | | MG. PER KG. | IN CONTROL | | | | IN PERIOD OF INJEC- TION | CHANGE IN R-T | | FIRST IN- CREASED P-R | | | MG. PER KG. | % OF FATAL DOSE | |
| | | | | | | | | | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | | | | | % OF FATAL DOSE |
| 1 | 2.36 | 100 | 190 | 165 | 0.077 | 0.085 | 0.091 | 64 | 64 | 12 | 42 | 64 | 64 | 64 | 61 | |
| 2 | 2.70 | 111 | 150 | 160 | 0.070 | --- | --- | --- | --- | --- | --- | --- | --- | 33 | 30 | |
| 3 | 1.68 | 111 | 260 | 200 | 0.068 | --- | --- | 41 | 37 | --- | --- | --- | --- | 58 | 52 | |
| 4 | 3.06 | 111 | 180 | 140 | 0.077 | 0.085 | 0.110 | 38 | 34 | 45 | 41 | 68 | 47 | 72 | 65 | |
| 5 | 2.00 | 115 | 230 | 180 | 0.068 | 0.075 | 0.100 | 30 | 26 | 70 | 61 | 74 | 62 | 70 | 61 | |
| 6 | 1.92 | 120 | 140 | 160 | 0.085 | --- | --- | 37 | 30 | --- | --- | --- | --- | 37 | 30 | |
| 7 | 3.86 | 120 | 190 | 210 | 0.073 | 0.080 | --- | --- | --- | 41 | 34 | --- | --- | 53 | 44 | |
| 8 | 2.70 | 122 | 165 | 130 | 0.080 | 0.091 | 0.110 | 36 | 30 | 50 | 48 | 73 | 66 | 59 | 48 | |
| 9 | 2.32 | 131 | 180 | 180 | 0.075 | --- | --- | 45 | 34 | --- | --- | --- | --- | 45 | 34 | |
| 10 | 2.00 | 135 | 220 | 160 | 0.079 | 0.093 | 0.105 | 30 | 22 | 81 | 60 | 60 | 54 | 93 | 60 | |
| 11 | 2.18 | 137 | 140 | 150 | 0.075 | 0.080 | 0.088 | 41 | 30 | 55 | 40 | 63 | --- | 73 | 53 | |
| 12 | 2.60 | 150 | 220 | 210 | 0.080 | 0.090 | 0.12-0.20 | 40 | 27 | 75 | 50 | 58 | --- | 64 | 43 | |
| 13 | 1.52 | 151 | 220 | 250 | 0.074 | 0.080 | 0.110 | 26 | 17 | 92 | 61 | 74 | --- | 98 | 65 | |
| 14 | 2.72 | 72 | 140 | 140 | 0.080 | --- | --- | --- | --- | --- | --- | --- | --- | 21 | 29 | |
| 15 | 2.42 | 111 | 185 | 150 | 0.072 | 0.080 | 0.115 | 41 | 37 | 70 | 63 | --- | --- | 90 | 89 | |
| 16 | 1.96 | 123 | 190 | 180 | 0.060 | --- | --- | 41 | 33 | --- | --- | --- | --- | 51 | 42 | |

TABLE III
CHLOROFORM FRACTION ("PURIFIED TINCTURE")

| NO. | WEIGHT OF ANIMAL | FATAL DOSE | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | FIRST IN- CREASED P-R | LONGEST P-R IN INJEC- TION | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | SLOWEST SINUS RATE | | ECTOPIC BEATS | |
|-----|------------------------|--------------------|--------------------|--------------------------------|------------------------------|-----------------------------|-------------------------------------|-------------------------------------|--------------------------|--------------------|-----------------------|--------------------------|-----------------------|--------------------|-----------------------|
| | | | IN CONTROL | IN PERIOD OF INJEC- TION | | | | CHANGE IN R-T | FIRST IN- CREASED P-R | | LONGEST P-R | SLOWEST SINUS RATE | | ECTOPIC BEATS | |
| | KG. | C.C. PER KG. | | | SEC. | SEC. | SEC. | C.C. PER KG. | % OF FATAL DOSE | C.C. PER KG. | % OF FATAL DOSE | C.C. PER KG. | % OF FATAL DOSE | C.C. PER KG. | % OF FATAL DOSE |
| 1 | 2.98 | 0.65 | 245 | 225 | --- | --- | --- | 0.15 | 23 | --- | --- | --- | --- | 0.35 | 54 |
| 2 | 2.06 | 0.68 | 220 | 190 | --- | --- | --- | --- | --- | --- | --- | --- | --- | 0.15 | 22 |
| 3 | 2.18 | 0.69 | 190 | 150 | --- | --- | --- | 0.14 | 20 | 0.28 | 40 | --- | 40 | 0.23 | 33 |
| 4 | 1.96 | 0.71 | 240 | 160 | --- | 0.078 | --- | 0.25 | 36 | 0.36 | 50 | --- | 50 | 0.36 | 50 |
| 5 | 3.40 | 0.90 | 210 | 170 | --- | 0.075 | --- | 0.18 | 20 | --- | --- | --- | --- | 0.25 | 28 |
| 6 | 2.06 | 0.92 | 190 | 150 | 0.095 | 0.090 | 0.095 | 0.34 | 37 | 0.48 | 53 | --- | 58 | 0.63 | 68 |
| 7 | 1.76 | 0.95 | 220 | 190 | --- | --- | --- | 0.31 | 32 | --- | --- | --- | --- | 0.67 | 70 |
| 8 | 2.80 | 0.96 | 230 | 155 | --- | 0.075 | 0.095 | 0.21 | 22 | 0.43 | 44 | --- | 56 | 0.48 | 50 |
| 9 | 1.42 | 1.00 | 210 | 190 | --- | 0.090 | --- | 0.24 | 24 | 0.48 | 48 | --- | --- | 0.62 | 62 |
| 10 | 2.56 | 1.00 | 210 | 172 | --- | 0.075 | --- | 0.24 | 24 | 0.29 | 30 | --- | --- | 0.35 | 35 |
| 11 | 1.94 | 1.43 | 190 | 140 | 0.100 | 0.090 | 0.100 | 0.32 | 23 | 0.55 | 39 | --- | 39 | 0.97 | 68 |

TABLE IV
TINCTURE ADONIS

| NO. | WEIGHT OF ANIMAL | FATAL DOSE | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | FIRST IN- CREASED P-R | LONGEST P-R IN INJEC- TION | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | | | SLOWEST SINUS RATE | | ECTOPIC BEATS | | |
|-----|------------------------|---------------|--------------------|---------------|------------------------------|-----------------------------|-------------------------------------|-------------------------------------|-------------------|-----------------------|--------------------------|-----------------------|----------------|--------------------------|-----------------------|-----------------------|-------------------|-----------------------|
| | | | MG. PER KG. | IN CONTROL | | | | IN PERIOD OF INJEC- TION | CHANGE IN RT-T | | FIRST IN- CREASED P-R | | LONGEST P-R | % OF FATAL DOSE | % OF FATAL DOSE | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE |
| | | | | | | | | | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 1 | 2.80 | 125 | 170 | 150 | 0.080 | 0.085 | --- | --- | 36 | 29 | --- | --- | 36 | 29 | --- | --- | | |
| 2 | 2.34 | 134 | 180 | 180 | 0.085 | 0.090 | 0.100 | 44 | 60 | 45 | 44 | --- | --- | 59 | 44 | --- | --- | |
| 3 | 3.44 | 142 | 235 | 195 | 0.070 | 0.080 | 0.095 | 46 | 64 | 45 | 55 | --- | --- | 78 | 55 | --- | --- | |
| 4 | 2.72 | 147 | 260 | 210 | 0.075 | --- | --- | --- | --- | --- | --- | 37 | --- | 73 | 50 | --- | --- | |
| 5 | 2.20 | 150 | 168 | 150 | 0.080 | --- | --- | 41 | --- | --- | --- | --- | --- | 93 | 62 | --- | --- | |
| 6 | 2.62 | 152 | 175 | 185 | 0.068 | 0.080 | --- | --- | 61 | 40 | --- | --- | --- | 91 | 60 | --- | --- | |
| 7 | 2.20 | 152 | 250 | 215 | 0.075 | 0.080 | 0.085 | 41 | 64 | 42 | 52 | --- | --- | 94 | 62 | --- | --- | |
| 8 | 2.50 | 152 | 210 | 205 | 0.065 | --- | --- | 41 | --- | --- | --- | --- | --- | 96 | 63 | --- | --- | |
| 9 | 3.46 | 156 | 230 | 140 | 0.078 | 0.085 | --- | 59 | 61 | 39 | 46 | 46 | --- | 48 | 31 | --- | --- | |
| 10 | 4.10 | 161 | 150 | 120 | 0.090 | 0.110 | --- | 24 | 74 | 46 | --- | --- | --- | 103 | 64 | --- | --- | |
| 11 | 3.66 | 169 | 185 | 140 | 0.075 | --- | --- | 59 | --- | --- | --- | --- | --- | 119 | 70 | --- | --- | |
| 12 | 2.42 | 175 | 200 | 145 | 0.080 | --- | --- | 72 | --- | --- | --- | --- | --- | 119 | 68 | --- | --- | |
| 13 | 2.78 | 201 | 225 | 195 | 0.070 | 0.090 | 0.120 | 48 | 80 | 40 | 48 | --- | --- | 80 | 40 | --- | --- | |

TABLE V
OUABAIN*

| NO. | WEIGHT OF ANIMAL | FATAL DOSE | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | FIRST IN- CREASED P-R | LONGEST P-R IN INJEC- TION | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | SLOWEST SINUS RATE | ECTOPIC BEATS | | |
|-----|------------------------|---------------|--------------------|--------------------------------|------------------------------|-----------------------------|-------------------------------------|-------------------------------------|-----------------------|--------------------------|-----------------------|--------------------------|------------------|-----------------------|-----------------------|
| | | | MG. PER KG. | IN PERIOD OF INJEC- TION | | | | CHANGE IN RT-T | | FIRST IN- CREASED P-R | | | LONGEST P-R | % OF FATAL DOSE | % OF FATAL DOSE |
| | | | | | | | | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE | | | | |
| 1 | 1.78 | 0.075 | 180 | 240 | 0.069 | --- | --- | 0.014 | 19 | --- | --- | --- | --- | 0.053 | 71 |
| 2 | 1.42 | 0.120 | 195 | 180 | 0.068 | --- | --- | 0.028 | 24 | --- | --- | --- | --- | 0.050 | 41 |
| 3 | 2.62 | 0.124 | 180 | 120 | 0.080 | 0.087 | --- | 0.054 | 43 | 0.070 | 54 | --- | 60 | 0.080 | 64 |
| 4 | 1.50 | 0.126 | 160 | 175 | 0.080 | 0.085 | --- | 0.013 | 11 | 0.066 | 53 | --- | --- | 0.093 | 74 |
| 5 | 2.64 | 0.132 | 190 | 110 | 0.074 | 0.079 | 0.085 | 0.040 | 30 | 0.054 | 40 | 55 | 55 | 0.086 | 65 |
| 6 | 2.44 | 0.135 | 200 | 190 | 0.073 | 0.080 | 0.090 | 0.045 | 33 | 0.069 | 51 | 66 | --- | 0.089 | 66 |
| 7 | 1.84 | 0.138 | 210 | 170 | 0.070 | 0.075 | --- | --- | --- | 0.079 | 58 | --- | --- | 0.092 | 67 |
| 8 | 1.74 | 0.139 | 160 | 100 | 0.065 | 0.070 | 0.085 | 0.071 | 51 | 0.077 | 56 | 66 | 66 | 0.064 | 46 |
| 9 | 2.24 | 0.143 | 240 | 140 | 0.069 | 0.075 | 0.120 | 0.072 | 50 | 0.085 | 60 | 70 | 70 | 0.100 | 70 |
| 10 | 1.84 | 0.146 | 220 | 180 | 0.080 | --- | --- | 0.038 | 26 | --- | --- | --- | --- | 0.065 | 44 |
| 11 | 2.60 | 0.155 | 200 | 120 | 0.070 | --- | --- | 0.077 | 49 | --- | --- | --- | --- | 0.091 | 59 |
| 12 | 2.42 | 0.186 | 230 | 200 | 0.070 | 0.075 | --- | 0.051 | 27 | 0.076 | 41 | --- | 56 | 0.116 | 63 |

*This specimen of ouabain was slightly yellowish.

*This specimen of ouabain was slightly yellowish, and as also indicated by the fatal dose it was probably not pure.

TABLE VI
DIGITOXIN (MERCK)

| NO. | WEIGHT OF ANIMAL | MINIMUM DOSE OF DRUG THAT PRODUCED: | | | | | | | | | | | | | | ECTOPIC BEATS | | |
|-----|------------------|-------------------------------------|-------------|--------------------|------------------------|------------------------|---------------------------|-------------|--------------------|-----------------|-------------|---------------------|-------------|-----------------|--------------------|-----------------|-------------|-----------------|
| | | FATAL DOSE | | SLOWEST SINUS RATE | | LONGEST P-R IN CONTROL | LONGEST P-R INCREASED P-R | LONGEST P-R | SLOWEST SINUS RATE | CHANGE IN RT-T | | FIRST INCREASED P-R | | LONGEST P-R | SLOWEST SINUS RATE | | | |
| | | KG. | MG. PER KG. | IN CONTROL | IN PERIOD OF INJECTION | SEC. | SEC. | SEC. | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE | MG. PER KG. | % OF FATAL DOSE |
| | | | | | | | | | | | | | | | | | | |
| 1 | 3.20 | 0.19 | 190 | 240 | 0.070 | 0.080 | --- | 0.03 | 17 | 0.11 | 57 | --- | --- | 0.10 | 50 | --- | --- | |
| 2 | 2.52 | 0.26 | 235 | 230 | 0.070 | 0.078 | 0.090 | 0.16 | 62 | 0.12 | 46 | --- | --- | 0.26 | 100 | --- | --- | |
| 3 | 1.92 | 0.34 | 260 | 260 | 0.070 | --- | --- | 0.16 | 46 | --- | --- | --- | --- | 0.26 | 67 | --- | --- | |
| 4 | 2.34 | 0.36 | 240 | 190 | 0.070 | --- | --- | --- | --- | 0.22 | 60 | --- | --- | 0.23 | 65 | --- | --- | |
| 5 | 3.46 | 0.38 | 160 | 200 | 0.080 | 0.12-0.18 | --- | 0.06 | 16 | 0.20 | 53 | --- | --- | 0.24 | 62 | --- | --- | |
| 6 | 3.12 | 0.38 | 190 | 160 | 0.080 | --- | --- | 0.07 | 18 | --- | --- | --- | --- | 0.18 | 47 | --- | --- | |
| 7 | 3.30 | 0.39 | 255 | 250 | 0.079 | --- | --- | 0.15 | 38 | 0.24 | 62 | --- | --- | 0.23 | 59 | --- | --- | |
| 8 | 2.62 | 0.40 | 225 | 230 | 0.075 | 0.085 | --- | 0.13 | 33 | --- | --- | --- | --- | 0.29 | 72 | --- | --- | |
| 9 | 2.88 | 0.41 | 200 | 190 | 0.065 | --- | --- | --- | --- | --- | --- | --- | --- | 0.17 | 41 | --- | --- | |
| 10 | 2.00 | 0.43 | 190 | 175 | 0.065 | --- | --- | --- | --- | --- | --- | --- | --- | 0.23 | 53 | --- | --- | |
| 11 | 2.86 | 0.44 | 200 | 200 | 0.080 | --- | --- | 0.15 | 34 | --- | --- | --- | --- | 0.27 | 62 | --- | --- | |
| 12 | 2.88 | 0.45 | 185 | 180 | 0.075 | 0.085 | --- | 0.17 | 37 | 0.27 | 59 | --- | --- | 0.32 | 69 | --- | --- | |
| 13 | 2.00 | 0.47 | 240 | 240 | 0.075 | 0.100 | --- | 0.15 | 32 | 0.27 | 58 | --- | --- | 0.30 | 64 | --- | --- | |

30 per cent of the fatal dose, while in the second a T-wave change appeared after 34 per cent, P-R lengthening after 41 per cent, and ectopic beats not until 65 per cent of the fatal dose had been injected. Animals 1 and 12 (Table II) each required 64 milligrams per kilogram to call forth ectopic beats, but the first required only 100 milligrams to cause death while the second required 150 milligrams. With the same preparations, doses that may serve merely to produce ectopic beats in some animals (animals 7 and 11 of Table III) may be sufficient to cause death in others (animals 1 to 8 of Table III). The appearance of ectopic beats may indicate a high degree of digitalis poisoning in some animals (89 per cent of the fatal dose in animal 15 of Table II), while in others, it may indicate a very early stage of digitalis action (29 per cent of the fatal dose in animal 14 of Table II). In the order in which the experiments of Table II were carried out it was a rather striking accident that five of the first seven figures for the production of ectopic beats were below 50 per cent whereas six of the following nine figures were above 50 per cent of the fatal dose.

TABLE VII

COMPARING DIFFERENT DIGITALIS BODIES WITH REFERENCE TO THE AVERAGE PERCENTAGE OF THE FATAL DOSE PRODUCING THE FIRST CHANGE IN VARIOUS ELECTROCARDIOGRAPHIC SIGNS

| SPECIMEN OF DRUG | CHANGE IN RT-T | FIRST INCREASED P-R | ECTOPIC BEATS |
|---------------------|-------------------|------------------------|------------------|
| Tr. Dig. (American) | 30 (24-37) | 47 (30-71) | 48 (30-75) |
| Tr. Dig. (German) | 32 (17-64) | 50 (34-63) | 51 (29-89) |
| Chloroform Fraction | 26 (20-37) | 43 (30-53) | 49 (22-70) |
| Tr. Adonis | 31 (15-41) | 41 (29-46) | 54 (29-70) |
| Ouabain | 33 (11-51) | 52 (40-60) | 61 (41-74) |
| Digitoxin | 33 (16-62) | 56 (46-60) | 62 (41-100) |
| Average | 31 | 48 | 54 |

The important data are summarized in Table VII. This shows the average percentage of the fatal dose of each of the preparations required to produce the first change in the RT-T, the first prolongation of the P-R interval, and ectopic beats. It is evident that each of these three phenomena is called forth by a percentage of the fatal dose that is the same for these six widely different members of the digitalis group. The figures (in parenthesis) showing the wide range of individual variations make it possible to understand better why no significance can be attached to the minor differences in the averages for the different preparations; namely, 26 to 33 per cent for the RT-T change, 41 to 56 per cent for the first increased P-R, and 48 to 62 per cent for the ectopic beat.

These results could be assumed to indicate directly the relative intensity of action of the digitalis bodies upon different cardiac structures only if each electrocardiographic sign represented an action

upon a single structure. The T-wave change produced by digitalis is probably due to a direct action upon the ventricle.⁴ We have already called attention to the facts that indicate that the prolongation of conduction time under the condition of our experiments was due in most instances to a peripheral depression of the A-V conducting system. In the case of the ectopic beats it was necessary to consider several structures. To illustrate, theoretically two specimens of the drug might produce ectopic beats with similar percentages of the fatal dose, yet the seat of action might be upon entirely different structures, because ectopic beats may be called forth by directly increasing the rhythmicity of the ventricle (or A-V node), by stimulation of the accelerator nerves, by suppression of the sinus through vagus stimulation, by the production of an A-V block, or by various combinations of these factors. As a matter of fact, the digitalis bodies do produce them in unanesthetized cats usually through a combination of these factors, the most important of which appears to be a direct action upon the ventricle (or A-V node) to increase its rhythmicity, and no essential differences in this respect were detected with different members of the digitalis group as shown in another study.⁵ It is safe to say, therefore, that as far as these experiments go, they indicate that different digitalis bodies act with essentially the same relative intensity (in relation to the fatal dose) upon different cardiac structures.

Robinson and Wilson⁶ found that approximately 25 per cent of a fatal dose of digitalis produced the first change in the T-wave, 50 per cent produced a definite change in the P-R interval and about 75 per cent called forth ectopic beats. In Table VII it is seen that our average for the T-wave change corresponds to theirs, but the other two phenomena occur with practically the same percentage of the fatal dose, namely, 48 and 54 per cent, instead of 50 and 75 per cent of the fatal dose as in their experiments. The figures in Tables I to VI that bear upon the relationship between the dosage required for the first prolongation of conduction and the production of ectopic beats have been further analyzed and the results summarized in Table VIII. It shows that in approximately one-half of the cases, conduction became prolonged before ectopic beats appeared, and in the other half the conditions were just reversed. Occasionally both phenomena were seen for the first time in the same tracing. When the increased P-R interval occurred first, it usually required from about 5 to 25 per cent of the fatal dose of additional drug to produce ectopic beats. When the ectopic rhythm occurred first, it was usually not possible to determine the conduction time except in occasional instances in which the abnormal rhythm was interrupted by a regular sinus rhythm in the tracing. It is probable that the lower average for the production of ectopic beats in our ex-

periments than in those of Robinson and Wilson is due, as we have shown in another study,⁵ to the fact that their animals were anesthetized with ether.

TABLE VIII

| SPECIMEN OF DRUG | NUMBER OF CASES IN WHICH | | |
|---------------------|---------------------------|------------------------------|---|
| | P-R CHANGE OCCURRED FIRST | ECTOPIC BEATS OCCURRED FIRST | BOTH OCCURRED FOR FIRST TIME IN SAME RECORD |
| Tr. Dig. (American) | 5 | 6 | 1 |
| Tr. Dig. (German) | 7 | 7 | 2 |
| Chloroform Fraction | 5 | 5 | 1 |
| Tr. Adonis | 5 | 6 | 2 |
| Ouabain | 5 | 7 | 0 |
| Digitoxin | 5 | 8 | 0 |

DISCUSSION

A stock argument found in commercial advertisements runs, "If digitalis is ineffective or badly tolerated" use this or that digitalis specialty. There are many papers in the literature indicating qualitative differences in the cardiac action of different digitalis bodies. In not a single case are the statements supported by satisfactory evidence. For example, Yamanouchi⁷ stated that strophanthus was three times as effective as digitalis (in proportion to the fatal dose) in causing cardiac slowing in the cat under ether anesthesia. An examination of his table shows that he obtained cardiac slowing after from 3 to 7 per cent of the fatal dose of his preparation of strophanthus. There is no statement as to the amount of slowing; and in view of the variability of the cat's heart rate during ether anesthesia, the depression of the vagus by ether, and the well-known fact that any considerable slowing of the cat's heart occurs only after more nearly 50 per cent of a fatal dose of digitalis, one can attach no significance to the results of such experiments.

Vaquez⁸ in the latest edition of his textbook (1924) stated that he found the margin of safety between the effective and toxic dose smaller for amorphous strophanthin than for ouabain (Arnaud), that both of these substances augment the "tonus" without acting upon the other functions of the myocardium, that he has never detected changes in conductivity or excitability, and that extrasystoles, so frequent after digitalis, are exceptional after these drugs. From his statements regarding dosage as well as from his conclusions regarding the mode of action of ouabain, it is apparent that Vaquez had used far too small doses of the drug, and that as far as indicating any qualitative differences in the cardiac actions of amorphous strophanthin, ouabain, and digitalis, it is hardly necessary to say that his views are wholly incorrect. One needs only to give a suitable dose of ouabain to a patient with auricular fibrillation and a rapid ventricular rate⁹ to

appreciate that ouabain does depress conduction in a very striking manner, or to give a suitable dose to an animal to see that the production of ectopic beats, so far from being rare, is impossible to avoid.

Langley¹⁰ used seven preparations of digitalis of different potencies in patients with auricular fibrillation. He attempted to correlate the degree of ventricular slowing and the production of vomiting with the biological potency of the drug. On the basis of the behavior of two or three patients in small groups after doses that were not comparable in activity he allowed himself to infer that the substance causing cardiac slowing is not identical with that producing the toxic effect (vomiting), that the toxic substance may be responsible for a high potency reading by biological assay while the drug may in fact be of low therapeutic value, that vomiting may result from this toxic factor before adequate therapeutic effects have occurred. The suggestion that the therapeutic action of digitalis is due to one substance and the toxic action (vomiting) to another, cannot be considered seriously in view of the fact that pure digitalis bodies like ouabain and digitoxin possess not only the therapeutic but the emetic action. It is of course conceivable that a preparation may be very active by intravenous injection in a bio-assay, and yet prove to be of low potency when given by oral administration to man because of a poorly absorbable fraction. Actually such conditions are exceedingly uncommon. Langley presents no satisfactory evidence to support his statement that some preparations of digitalis are so actively emetic that vomiting is produced before sufficient drug is present to produce the therapeutic effects. It would be necessary to show with suitable controls that other preparations would produce the therapeutic effects without emesis in the same patients. The question that has been raised, however, involves a matter of very great practical importance because it is not difficult to find clinical cases which on the surface seem to indicate that the emetic action of a specimen of the drug is preventing effective digitalization. For example, digitalis often fails to check the progress of failure in the terminal stage of heart disease.³ If the drug is continued or administered in larger doses in an effort to relieve symptoms, toxic effects are often induced though no therapeutic effects are in evidence. It is clear that the drug is not at fault in such cases.

Hatcher and Eggleston¹¹ have shown that the relative emetic activity of the various members of the digitalis group shows considerable differences when the drug is given intravenously in animals. Thus true digitalin caused vomiting with an average of 22 per cent of the fatal dose, while the average for the specimen of digitalis they employed was 46 per cent of the fatal. There is no evidence at present as to whether different specimens of digitalis itself show differences in their relative emetic activity.

The observations that one preparation of digitalis has produced more satisfactory therapeutic results or less toxic effects than another require very close scrutiny because there are many factors which if left out of consideration may lead to erroneous conclusions. In a few instances in which one of us (H. G.) has had an opportunity to examine in detail or to check the evidence for such statements there has usually appeared to be some factor not inherent in the drug. Improper dosage seems to be the most common source of error; preparations are assumed to show differences in their cardiac actions when they have not been used in strictly comparable doses in terms of effects upon patients. In one case a patient was digitalized fully (to the point of minor toxic symptoms) by a tincture of digitalis, and there was little or no improvement in the symptoms of congestive heart failure. After a period of about two weeks the patient was fully digitalized by a proprietary preparation, and marked improvement resulted. This was interpreted by the physician as an indication that the one preparation had a greater relative therapeutic activity than the other. Yet it is not uncommon that a patient fails to improve appreciably after the first course of digitalization but shows striking improvement after a second course a week or two later with the *same preparation*. This can be demonstrated in patients after a period of control in bed without medication, during which time a constant level in the general condition has been reached (water intake and output, body weight, heart rate, symptoms).

The three specimens of digitalis, "A," "B," and "C," submitted by Professor Magnus for the Hygiene Committee of the League of Nations, were tested in various clinics and laboratories. A clinical study of these specimens on a relatively small group of patients was reported by Martin¹² of Baltimore and on a larger group by Gilchrist and Lyon¹³ of Edinburgh. Martin found that the therapeutic effects appeared before any symptoms or signs of digitalis intoxication in practically every case, while Gilchrist and Lyon were troubled by the occurrence of nausea and vomiting especially with specimens "B" and "C" before one-half of the total dose had been administered which they attributed to a local irritant action. In both studies the powdered leaf was employed in large doses. Martin's patients received the drug in small capsules of 0.2 gram each, while those of Gilchrist and Lyon received bulky cachets which they state some patients had difficulty in swallowing. This may have been a factor in producing the nausea and vomiting. Sufficient data are not given for a more precise comparison of the technic of administration. In any event, that specimens "B" and "C" were more irritant to the stomachs of Englishmen than to those of Americans is much less likely than the assumption that nausea and vomiting were due to some factor other than the direct irritation of the stomach by the drug.

Two commercial specimens were employed in a study of digitalis in pneumonia.¹⁴ When comparable doses of the two specimens were given in terms of their supposed potency, about one-half of the patients vomited after one of the specimens and very few vomited after the other. This suggested that one specimen was more actively emetic than the other in relation to the fatal dose for animals. When the two were tested it was found that the one which caused the vomiting had been incorrectly labelled by the manufacturer and that therefore the vomiting was not due to a greater relative emetic activity but that the patients had really received about twice as much digitalis as was indicated in terms of activity. These instances are cited merely to call attention to the numerous factors that may give rise to apparent differences in the action of various specimens of digitalis and the dangers attending the interpretation of observations that appear to indicate essential differences in the cardiac action of different members of the digitalis group.

In the present study we have not examined all the actions of the digitalis bodies, not even the most important one, namely, that action directly upon the heart which improves myocardial efficiency in congestive heart failure (the improvement may be the result of a number of direct and indirect actions). We have, however, compared a number of cardiac actions within both the therapeutic and toxic range of widely different digitalis bodies, and the results show that these act with the same relative intensity upon different cardiac structures. A critical appraisal of any data purporting to show essential qualitative differences between digitalis bodies must not fail to take cognizance of the extreme variability of the reaction of *different individuals* toward the *same preparation* injected in the same way. As we have already shown the law of chance under these conditions sometimes juggles the data in such a way as to make it difficult indeed to escape erroneous conclusions.

SUMMARY

In the present study seventy-seven experiments were carried out with six widely different members of the digitalis group in order to ascertain whether these showed any qualitative differences in the cardiac action. Electrocardiographic criteria of digitalis action were used, and the relative intensity of action upon different cardiac structures (in relation to the fatal dose) was used to indicate qualitative differences.

The results show that widely different digitalis bodies have the same qualitative cardiac actions but that there are extraordinary individual differences in response to the same preparation. This fact may be an important factor in the confusion found in the clinical literature.

There are numerous references in the literature to qualitative dif-

ferences in the cardiac action of different members of the digitalis group, and implications that such differences exist are common in commercial advertisements, but in no single instance are these statements substantiated by adequately controlled experiments.

Examples are cited showing some of the sources of error in the interpretation of observations which appear to indicate qualitative differences in the cardiac action of different digitalis bodies.

REFERENCES

1. Hatcher, R. A.: J. A. M. A., 75: 463, 1920.
2. Gold, H., Gryzwacz, P. L., and Nowicki, V. A.: AM. HEART J. 4: 336, 1929.
3. Gold, H., and Otto, H.: AM. HEART J., 1: 471, 1926.
4. Cohn, A. E., Fraser, F. R., and Jamieson, R.: J. Exper. Med., 21: 593, 1915.
5. Gold, H., Lieberman, A., and Gelfand, B.: In press.
6. Robinson, G. C., and Wilson, F. N.: J. Pharm. & Exper. Therap., 10: 491, 1918.
7. Yamanouchi, K.: Tohoku J. Exper. Med., 9: 111, 1927.
8. Vaquez, H.: Diseases of the Heart, Philadelphia, 1924, p. 688, W. B. Saunders Co.
9. Wyckoff, J., and Goldring, W.: Arch. Int. Med., 39: 488, 1927.
10. Langley, G. J.: Proc. Royal Soc. Med., 21: 1067, 1928.
11. Hatcher, R. A., and Eggleston, C.: J. Pharm. & Exper. Therap., 4: 113, 1912.
12. Martin, L. E.: J. Pharm. & Exper. Therap., 31: 229, 1927.
13. Gilchrist, A. R., and Lyon, D. M.: J. Pharm. & Exper. Therap., 31: 319, 1927.
14. Wyckoff, J., Gold, H., and Travell, J. G.: AM. HEART J., 5: 401, 1930.

THE HEART IN THROMBO-ANGIITIS OBLITERANS*

SAUL S. SAMUELS, M.D., AND SYDNEY C. FEINBERG, M.D.
NEW YORK, N. Y.

WITH more intensive study of thrombo-angiitis obliterans, evidence is accumulating which points to the fact that this disease is not always limited to the peripheral blood vessels. It is becoming increasingly evident that there may be simultaneous involvement of arteries in other parts of the body. The occasional complaint of anginal symptoms in some of our patients suffering from thrombo-angiitis suggested to us the systematic study of a series of fifty consecutive cases of this disease in order to determine the incidence of cardiac lesions.

In this research we have avoided, as far as possible, the inclusion of cases of peripheral atherosclerosis. In some instances the differential diagnosis between atherosclerosis and thrombo-angiitis obliterans has been difficult, but wherever any doubt as to classification arose, the case was not included in this series. The simultaneous occurrence of peripheral atherosclerosis with coronary artery sclerosis is a well-established fact and will not be discussed in this communication. The possibility of atherosclerosis superimposed upon thrombo-angiitis obliterans must also be considered in the case of older individuals.

The patients comprising this group were, for the most part, young males. In every case the onset of symptoms in the extremities was prior to the age of 45 years. Every patient presented conclusive evidence of peripheral arterial disease, which, as far as our present knowledge goes, we believe to be thrombo-angiitis.

Each patient had been a heavy cigarette smoker for a number of years. Nine of these fifty cases (eighteen per cent) had had superficial migrating phlebitis of the extremities at some time during the course of the illness. Of these nine cases, two were in the group with cardiac lesions. In no instance was there a history of lues, nor was the Wassermann reaction positive in any case.

While we have been concerned, primarily, with the detection of involvement of the coronary arteries in the disease process known as thrombo-angiitis obliterans, the difficulty of establishing this fact by clinical study alone has been constantly recognized. The ultimate diagnosis of thrombo-angiitis obliterans from the pathological standpoint rests upon the discovery of the typical inflammatory lesion in the blood vessels, which, in the case of coronary arteries can be obtained only at autopsy. Clinically, the diagnosis of coronary artery disease is justified when electrocardiographic study reveals certain changes

*From the Mount Sinai Hospital, New York.

from the normal. These changes are assumed to be the result of disturbances of the myocardium and conduction system of the heart produced by interference with blood supply from the coronary arteries.

The cardiac status of each patient was investigated under the following headings: (1) Subjective cardiac symptoms. (2) Physical examination of the heart. (3) X-ray examination of the heart. (4) Electrocardiography.

The subjective symptoms of coronary artery disease were considered from the standpoint of the symptom-complex known as angina pectoris in its various manifestations, such as precordial pain, substernal distress, choking or constricting dyspnea. As pointed out by Libman, dyspnea on exertion may be complained of, and not pain. If, however, the patient is not very hyposensitive, he may feel pain. Further evidence of myocardial damage was sought in the physical examination. The character of the apical impulse was observed. Cardiac outlines were noted, although enlargement of the heart borders has been found to have no specific value in the determination of coronary disease. Feeble heart sounds were considered suggestive of myocardial change. Gallop rhythm is of importance as a diagnostic sign. Murmurs were considered of no confirmatory value in determining the presence of myocardial or coronary disease. Bilateral blood pressure readings were made. Teleroentgenograms were used to detect abnormalities of the cardiac outlines.

In this study, the greatest stress was placed upon the electrocardiogram. Due cognizance was taken of the fact that rheumatic fever may be responsible for almost any type of electrocardiographic change, but since none of our cases have at any time manifested this disease, we feel that this factor may be disregarded in the present study.

The accepted changes in the electrocardiogram indicative of myocardial change are the following:

(1) Intra-ventricular conduction defects as described by Oppenheimer and Rothschild. These include prolongation of the QRS interval and distortion of QRS complexes which must be observed in several examinations.

(2) Changes in the T-wave. Negative T-waves in more than one lead are suggestive. According to Pardee, the cove plane T-wave is definite evidence of coronary involvement.

(3) Arrhythmias, while not specific, were considered in the final determination of whether or not myocardial damage was present.

Of the fifty cases studied, five showed definite evidence of myocardial disturbance which we attributed to a probable underlying coronary artery disease. Of the remaining forty-five cases, thirty did not present sufficient evidence. While fifteen cases were entirely negative, it must not be forgotten that coronary disease may be present without yielding any clinical or electrocardiographic manifestation.

A synopsis of the records of the five patients showing evidence of myocardial damage follows:

CASE REPORTS

A. S.—Case No. 20. The patient was a Russian Jew, 52 years old. At the age of 38 years he developed an ulcer of the left foot. This lesion apparently marked the onset of thrombo-angiitis obliterans. Twelve years later the left leg was amputated because of extensive gangrene. Subsequently the patient developed typical lesions of thrombo-angiitis obliterans in the upper extremities. For the past year the patient noticed precordial pressure and lassitude. At times the pressure was intensified into a real pain. There was occasional dyspnea on exertion. Examination revealed poor heart sounds. The apex beat was felt in the 5th interspace. The left border was 12.5 cm. from the midline. No murmurs were heard. Blood pressure was 130/90 mm. in both arms. X-ray examination of the heart and lungs was negative. Electrocardiographic examination showed a thickening of QRS complexes, particularly in Lead III. Their interval measured



Fig. 1.—A. S. Case No. 20. Moderate thickening of the QRS complexes in all the leads. Their interval measures 0.10-0.12 of a second. T-waves are sharply inverted in Lead III.

0.10-0.12 of a second. The T-waves were sharply inverted in Lead III and had the appearance usually seen after a recent coronary closure.

I. T.—Case No. 27. A man of 40 years whose symptoms of thrombo-angiitis obliterans began at the age of 38. Examination showed marked closure of the arteries of the upper extremities and also of the lower extremities. He had had dyspnea on exertion and palpitation. The heart sounds were weak. X-ray examination showed a peculiar cardiac outline suggestive of myocardial disease. Electrocardiographic examination showed low voltage in all leads and thickening and widening of the QRS complexes, indicative of intra-ventricular conduction defect.

J. F.—Case No. 30. A Russian Jew, aged 31 years, first came under our care January 4, 1926, complaining of pain in the right foot of 15 years' duration. He had been a heavy cigarette smoker for many years. Examination showed bilateral involvement of both lower extremities. His only cardiac symptom when first seen was dyspnea on exertion. At subsequent examinations he began to complain of attacks of precordial pain radiating to the back. He also noticed occasional palpitation. Physical examination showed only a slight enlargement of the cardiac outline particularly toward the left. This was confirmed by x-ray examination. Electrocardiographic examination on January 4, 1926, revealed the fact that the

S-T interval did not reach the iso-electric level in Leads II and III. This phenomenon appeared in the second examination on January 5, 1926. One year later the electrocardiogram showed left ventricular preponderance and a cove plane T-wave

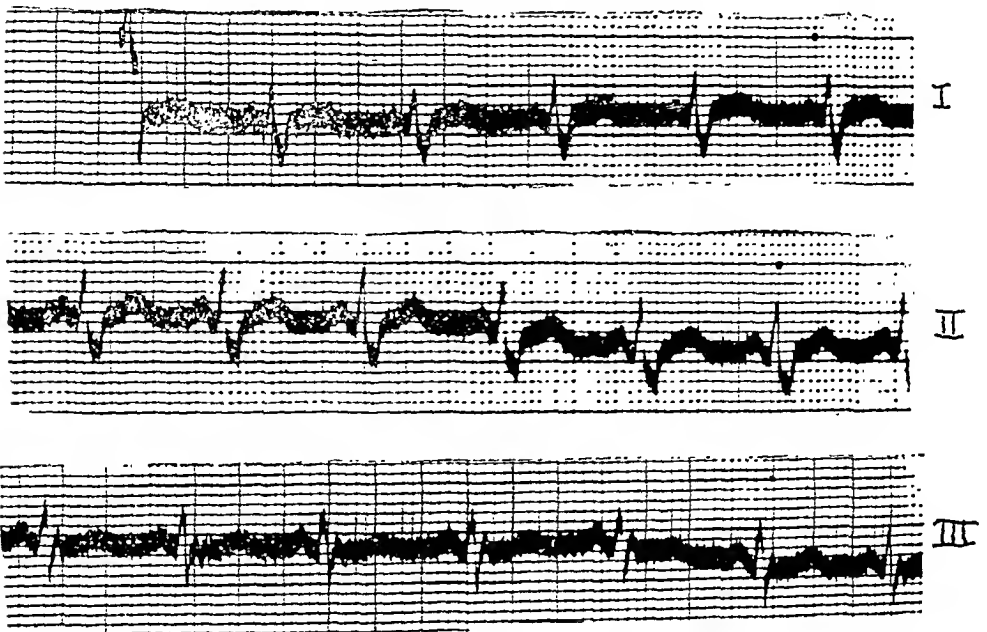


Fig. 2.—I. T. Case No. 27. Thickening and widening of the QRS complexes (intra-ventricular conduction defect).

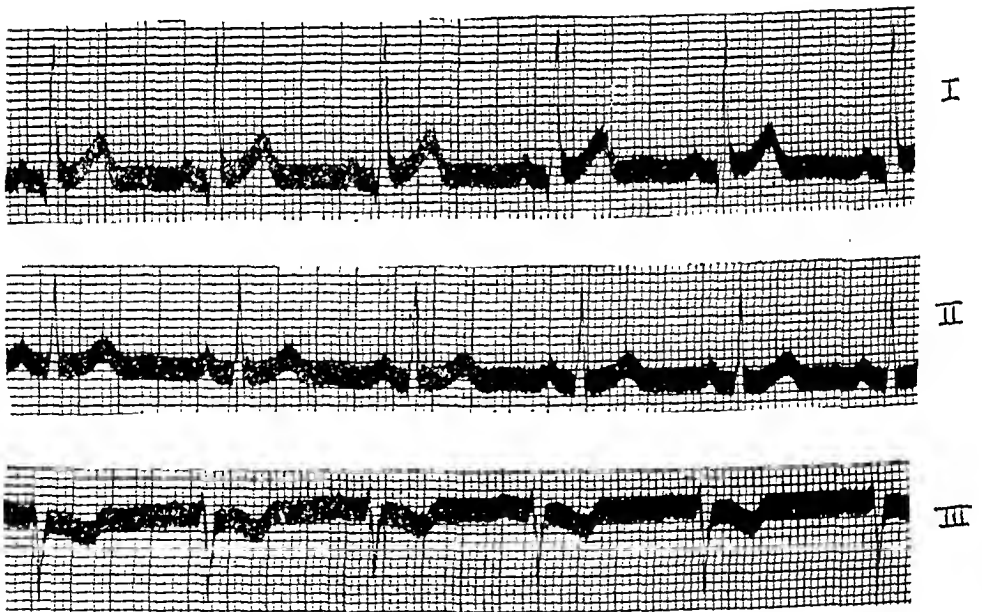


Fig. 3.—J. F. Case No. 30. Left ventricular preponderance. T-waves are sharply inverted in Lead III and are of the cove plane type. S-T transition in Lead I does not quite reach the iso-electric level (myocardial?).

in Lead III. Again it was observed that the S-T interval did not reach the iso-electric level in Lead I.

J. L.—Case No. 50. This patient was a man of 36 years, born in Russia. The onset of symptoms of thrombo-angiitis obliterans occurred in the right leg at the

age of 27. Amputation of this leg was performed 3 years later. The patient subsequently developed lesions in the left leg and in the right upper extremity. He has had frequent attacks of migrating phlebitis in the legs. About 9 years after the

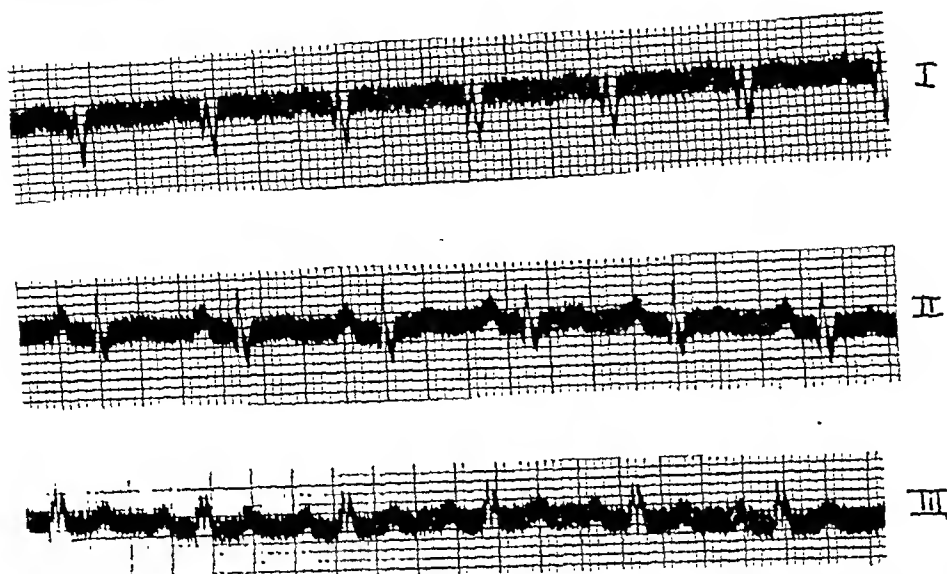


Fig. 4.—J. L. Case No. 50. Right ventricular preponderance. QRS interval measures 0.09 of a second with notching in all leads. Low voltage (intraventricular block).

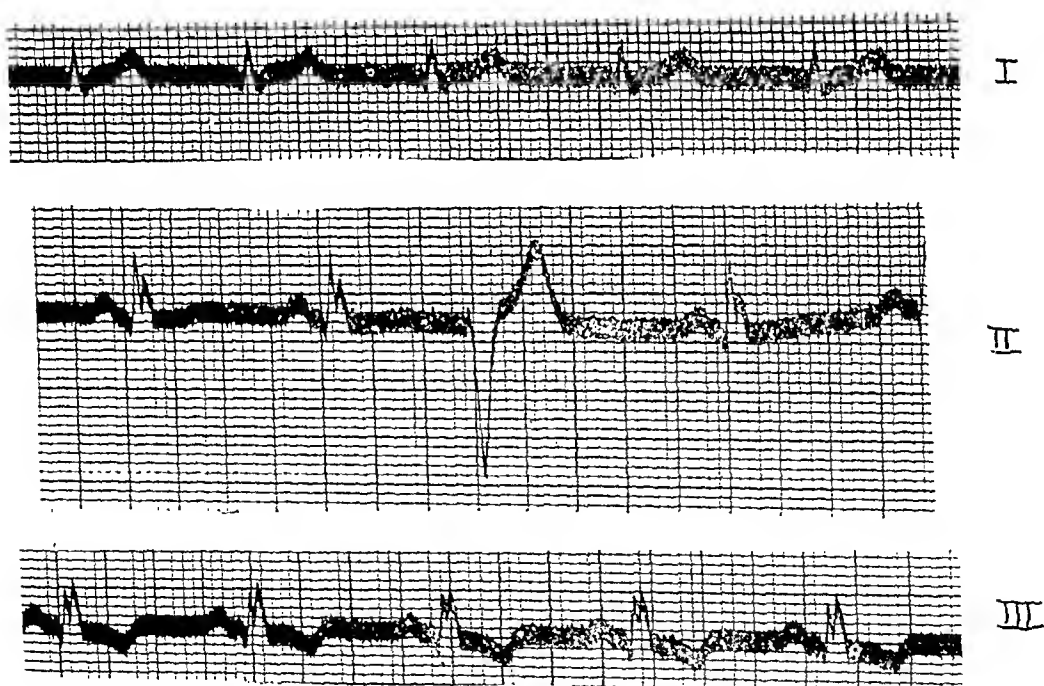


Fig. 5.—Intraventricular conduction defect (arborization block) T₂ negative. Occasional ventricular extrasystole.

onset the patient began to have attacks of sub-sternal pain radiating through to the back. These pains were burning in character and were occasionally associated with vomiting. During some of these attacks the pain radiated down both arms. Soon after this the patient began to complain of dyspnea on exertion. Examination revealed extensive closure of the arteries of both legs and partial occlusion in the

TABLE I

| CASE NO. | AGE | CARDIAC HISTORY | CARDIAC EXAM. | B.P. | X-RAY | ECG |
|----------|-----|------------------------------|---------------------------------|---------|--|---|
| 1 | 43 | Negative | Negative | 130/90 | Negative | LVP. |
| 9 | 55 | Negative | Negative | 145/100 | Heart enlarged to left | LVP. T ₂ negative. QRS 0.09 sec- ond with slight notching |
| 14 | 36 | Negative | A ₂ sounds increased | 135/95 | Negative | LVP. |
| 17 | 44 | Precordial pain | Sounds poor at base | 120/80 | Negative | Slight thickening of QRS. LVP. |
| 19 | 30 | Negative | Negative | 160/95 | Negative | Negative |
| 20 | 52 | Precordial pain | Poor heart sounds | 130/90 | Negative | plexes notched |
| 21 | 42 | Palpitation | Aortic diastolic | 165/105 | Negative | T negative in Lead III. QRS com- |
| 23 | 44 | Negative | Negative | 105/75 | Negative | Negative |
| 24 | 39 | Precordial pain | Negative | 120/90 | Negative | Low voltage all leads |
| 26 | 33 | Negative | Negative | 140/100 | Negative | Negative |
| 27 | 39 | Dyspnea and pal- pitation | Negative | 125/80 | Cardiac outline sug- gestive of myo- cardial disease | Low voltage. Intraventricular conduction defect |
| 28 | 47 | Negative | Negative | 140/80 | Slight general car- diac enlargement suggestive of myo- cardial disease | LVP. in Lead II. S-T transition does not reach level |
| 29 | 33 | Moderate dyspnea | Negative | 155/110 | Negative | LVP. |
| 30 | 31 | Dyspnea on exer- tion | Negative | 135/115 | Hypertrophy left ventricle | In Leads II and III S-T does not quite reach iso-electric level |
| 32 | 37 | Precordial distress | Negative | 165/90 | Negative | LVP. |
| 36 | 27 | Dyspnea on exer- tion | Negative | 115/85 | Negative | LVP. |

TABLE I—CONT'D

| CASE NO. | AGE | CARDIAC HISTORY | CARDIAC EXAM. | B.P. | X-RAY | ECG |
|----------|-----|-------------------------|---------------------|---------|--|---|
| 37 | 41 | Negative | Negative | 120/ 85 | Negative | Negative |
| 39 | 30 | Negative | Negative | 135/115 | Negative | LVP. T ₂ slightly inverted |
| 45 | 45 | Negative | Negative | 145/100 | Negative | LVP. Diphasic QRS in Lead I. Slight |
| 50 | 36 | Palpitation and dyspnea | Negative | 120/ 85 | Hypertrophy and dilatation of left ventricle | covering of S-T transition in Lead III |
| 51 | 39 | Negative | Sounds poor at base | 140/ 90 | Slight general cardiac enlargement | LVP. Inversion of T ₂ |
| 52 | 43 | Negative | Negative | 145/ 90 | Negative | Negative |
| 53 | 52 | Preordial pain | Negative | 160/100 | Negative | Negative |
| 54 | 40 | Negative | Negative | 135/ 80 | Negative | Negative |
| 54 | 53 | Negative | Negative | 140/ 80 | Negative | Slight inversion T-waves in Lead III |
| 62 | 29 | Negative | Negative | 130/ 85 | Negative | Negative |
| 63 | 34 | Negative | Negative | 135/ 85 | Negative | Negative |
| 65 | 32 | Negative | Poor at base | 130/ 70 | Negative | Negative |
| 67 | 35 | Negative | Negative | 140/ 90 | Slight cardiac enlargement | Slight thickening of QRS complexes in all leads |
| 71 | 44 | Negative | Negative | 125/ 70 | Negative | Negative |
| 84 | 46 | Negative | Negative | 155/100 | Moderate aortic enlargement | Slight inversion of T ₂ |
| 89 | 34 | Negative | Negative | 130/ 85 | Slight enlargement to the left suggesting myocardial disease | T ₂ negative. Rate 106 |

TABLE I—CONT'D

| CASE NO. | AGE | CARDIAC HISTORY | CARDIAC EXAM. | B.P. | X-RAY | ECG |
|----------|-----|---|---|---------|---|---|
| 100 | 33 | Negative | Poor heart sounds | 130/ 80 | Negative | Tendency to LVP. |
| 107 | 62 | Negative | Apical systolic | 170/ 95 | Negative | Negative |
| 116 | 35 | Negative | Negative | 135/100 | Negative | T ₃ inverted |
| 114 | 42 | Negative | Negative | 110/ 70 | Negative | Negative |
| 117 | 45 | Negative | Negative | 130/ 85 | Negative | R-waves low in all leads |
| 119 | 35 | Negative | Apical systolic mur- | 130/ 80 | Negative | Low voltage in Lead III |
| | | | mur | | | |
| 124 | 41 | Negative | Negative | 150/ 80 | Negative | LVP. |
| 131 | 44 | Negative | Negative | 190/100 | Negative | LVP. |
| 132 | 48 | Precordial pain 5 yrs. Dysp- nea on exer- tion | Mitral presystolic and aortic dias- tolic murmurs | 155/ 90 | Hypertrophy left ventricle, moderate dilatation of aortic arch | LVP. T ₃ negative |
| 133 | 47 | Negative | Negative | 140/ 90 | Negative | LVP. |
| 137 | 35 | Negative | Negative | 125/ 85 | Negative | Negative |
| 142 | 38 | Negative | Negative | 170/ 90 | Negative | Negative |
| 147 | 47 | Negative | Heart enlarged to left | 120/ 85 | Negative | LVP. T ₃ negative |
| 150 | 40 | Negative | Negative | 160/110 | Negative | LVP. Negative T ₃ |
| 152 | 45 | Precordial pain. Dyspnea and palpitation | Mitral systolic mur- mur | 150/ 90 | Negative | Slight inversion of T ₃ |
| 156 | 31 | Palpitation and dyspnea | Negative | 135/ 85 | Negative | Negative |
| 157 | 56 | Precordial pain. Dyspnea | Poor heart sounds | 170/110 | Negative | Intraventricular conduction defect in Lead III |

upper extremities. The heart was not enlarged. Cardiac sounds were all of fair quality. No murmurs were heard. The lungs were clear. X-ray examination of the chest showed moderate hypertrophy of the heart with dilatation of the left ventricle. Electrocardiographic examination showed right ventricular preponderance. QRS interval measured 0.09 of a second with notching in all leads and low voltage. The above indicates intra-ventricular block. (Arborization block of Oppenheimer and Rothschild.)

D. F.—Case No. 157. A Russian Jew, 56 years old. Symptoms of thrombo-angiitis obliterans began at the age of 25 with migrating phlebitis of the right leg. This was followed 4 years later by intermittent claudication, and gangrene of the right leg. Amputation of the right leg was then performed. Ten years ago the patient developed similar pains in the left leg. Gangrene and amputation followed. For the past 5 years he had noticed precordial pain and dyspnea on slight exertion. Electrocardiographic examination showed an intra-ventricular conduction defect (arborization block). T_2 negative. Occasional ventricular extrasystole.

SUMMARY

Fifty cases of thrombo-angiitis obliterans were studied from the standpoint of coronary artery involvement. Five of these cases showed definite clinical and electrocardiographic evidence of myocardial damage, presumably due to coronary artery lesions. Thirty of these cases showed minor evidence, insufficient for the diagnosis of coronary artery damage. Fifteen of these cases showed no clinical evidence of myocardial or coronary artery lesions.

An accurate diagnosis of thrombo-angiitis obliterans of the coronary arteries is permissible only after demonstration of the typical arterial lesion at autopsy.

We wish to thank Dr. Irving Roth, Dr. Emanuel Libman and Dr. B. S. Oppenheimer for their kind cooperation.

HEART DISEASE IN THE ROCKY MOUNTAIN REGION

L. E. VIKO, M.D.
SALT LAKE CITY, UTAH

VARIOUS writers have suggested the need for data on the incidence and etiology of heart disease in different sections of the country.¹ No such information for the Rocky Mountain region has yet been published. For these reasons certain facts regarding heart disease in Utah, Idaho and Wyoming are presented, and comparison is made with similar data from a few other sections.

Utah, Idaho and Wyoming, lying largely among the Rocky Mountains, are similar in geography, climate and population. The facts available show no significant differences in heart disease between these states. They lie at a high altitude and have a low average annual rainfall despite marked change of seasons. The density of population is very low; according to the census of 1920 there were only eight cities in the three states that had populations of over 10,000. Salt Lake City, the largest of them, had an estimated population in 1929 of 138,000. In 1923 only 8.5 per cent of the population of Idaho, 14.3 per cent of that of Wyoming and 36.2 per cent of that of Utah were classed as urban. This is to be compared with 78.9 per cent for New York and 82.4 per cent urban for Massachusetts.² In the Rocky Mountain states there is relatively little poverty or crowded living conditions. The colored population in 1923 comprised less than 2 per cent of the total.⁴ The foreign-born population in 1923 averaged less than 17 per cent.³ Nearly 40 per cent of the population is engaged in agriculture, forestry or animal husbandry.⁴ These states present many contrasts with eastern and southern sections, and it was thought of possible interest to learn whether there were any corresponding differences in the heart disease situation.

Mortality.—The cardiac mortality rates for Utah, Idaho and Wyoming are among the lowest state rates in the country. In 1927 they ranked thirty-first, thirty-fifth and thirty-ninth respectively⁶ (Fig. 1). Approximately the same relative positions held true for 1921,⁵ 1923² and 1925.⁵ These relatively low rates are not peculiar to heart disease, as the rates in the three states were also comparatively low for the other major causes of death and for all causes.

It would be of interest to know whether the proportion of deaths from each etiologic type is the same in the states with high and low cardiac mortality; whether the differences between states in total cardiac mortality could be associated with corresponding differences in only one of the etiologic types such as the rheumatic or the arteriosclerotic. Unfortunately mortality statistics as at present reported

do not furnish such data. A suggestive correlation is obtained by comparing for each state the proportion of cardiac deaths occurring at the younger ages with the total cardiac mortality. The year of 1923 was chosen as presenting for most states a fair representation of the mortality trend. The deaths under the age of forty-five years were arbitrarily chosen because mortality and population statistics were readily available for this age group. Cardiac deaths under forty-five years of age indicate roughly enough, it is true, deaths largely from rheumatic heart disease in contrast with the deaths over forty-five years from the degenerative types of heart disease. Such a comparison showed that in general the higher the total cardiac mortality rate, the lower the proportion of cardiac deaths under the age of forty-five years (Fig. 1). (An approximately parallel but lower curve could be drawn for deaths under thirty-five years of age.) The significance of such a comparison becomes less, however, if we compare the cardiac death rate under forty-five years per 100,000 population living under the age of forty-five years with the total cardiac mortality rate (Fig. 1). It now becomes apparent that the age distribution of the living population explains at least in part the supposed inverse ratio between total cardiac mortality and cardiac mortality under the age of forty-five years. It is curious to note the relatively high cardiac mortality under the age of forty-five years in the states of Louisiana and Florida where rheumatic heart disease is supposed to be less frequent than in northern states.

As a corollary to this it seems that there is a significant relation between the total cardiac mortality of each state and the living proportionate population over the age of forty-five years in each state (Fig. 2).

It has been shown that in the registration area the urban cardiac mortality rate has remained each year appreciably higher than the rural one.⁵ So it is of interest to note that there is a rough correlation between the cardiac mortality of the states and their percentage urban population (Fig. 2). No such relation could be shown between mortality rates and density of population.

In Utah the cardiac mortality by years has been rising in a manner more or less similar to that of other states and of the registration area (Fig. 3). Idaho and Wyoming have been included in the registration area for too short a period to justify comparison. The mortality rate for Salt Lake City has been rising as in other cities of the country.

As elsewhere the urban cardiac mortality rates of Utah, Idaho and Wyoming are higher than the rural ones. In each of the three states and in Salt Lake City as elsewhere heart disease is the principal cause of death.

Etiology.—In order to secure data regarding the etiology of heart disease in this section of the country a study has been made of 1000

Cardiac deaths under age 45—percentage of total cardiac deaths

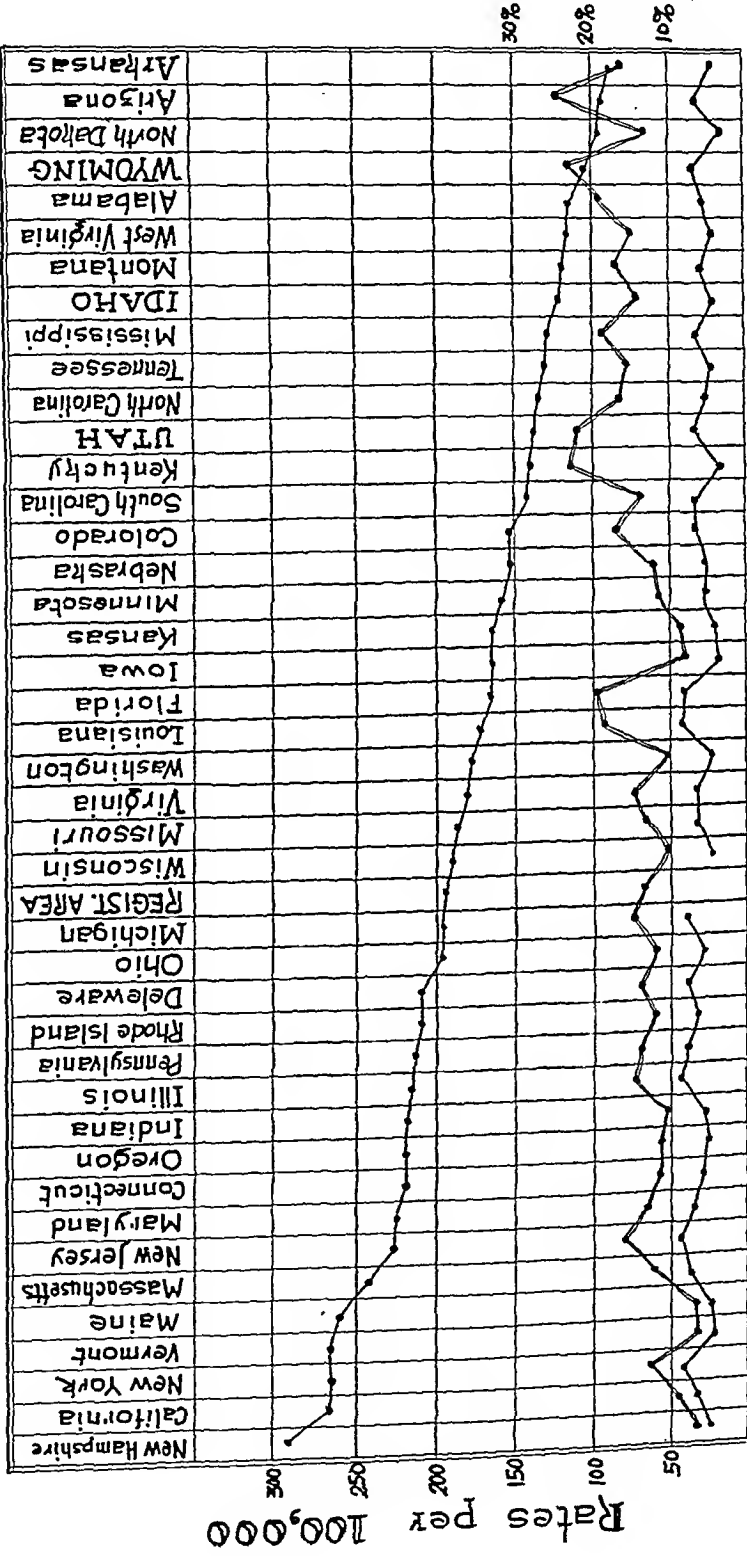
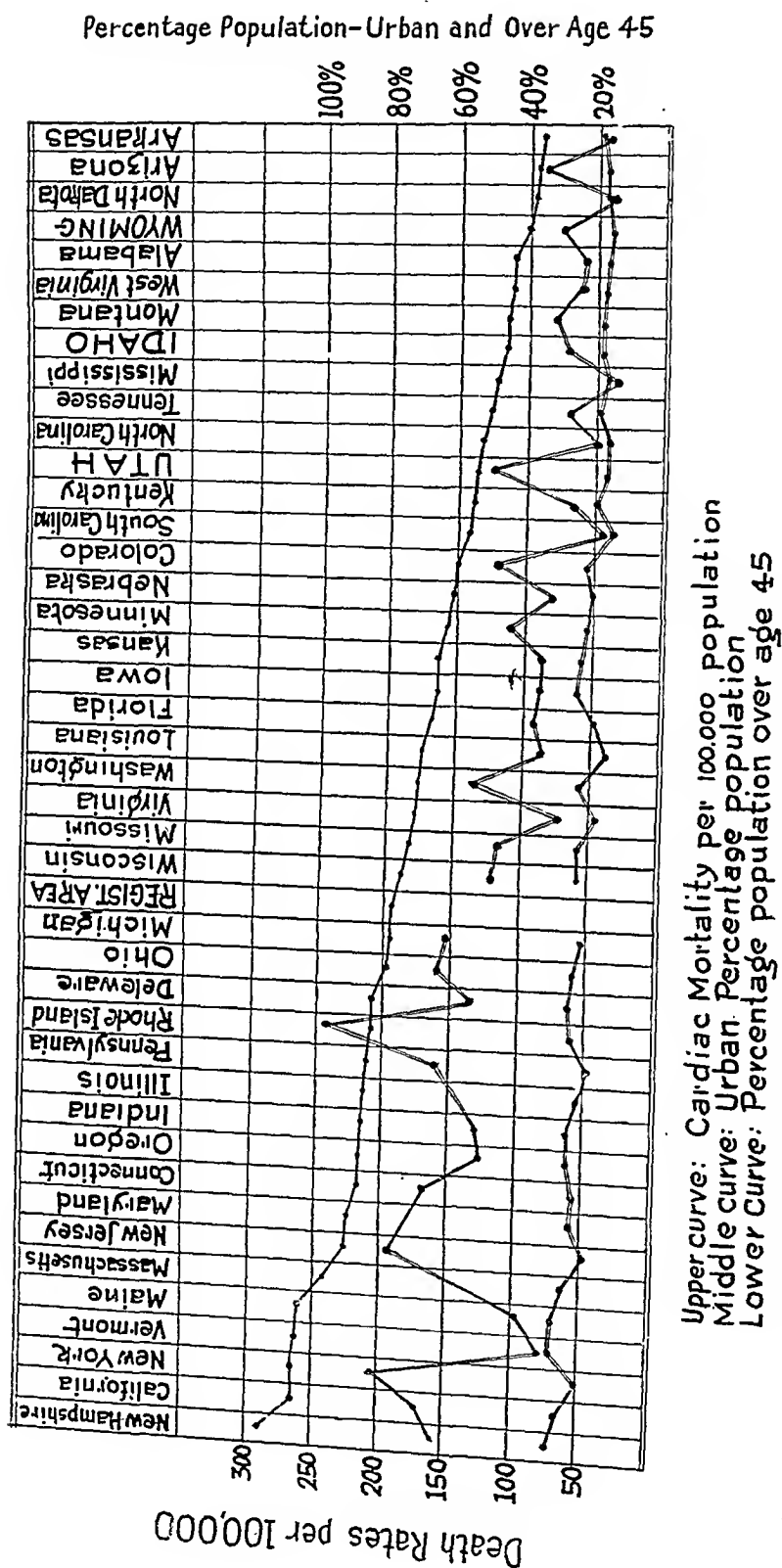


Fig. 1.—Mortality rates by states from heart disease (Code 87-90).



cases of heart disease or disorder occurring in this Rocky Mountain region. All the cases were studied by myself, by my associate Dr. W. R. Tyndale or by both of us, thus insuring uniformity of diagnosis. The diagnostic criteria were those proposed by the Heart Committee of the New York Tuberculosis and Health Association.⁷ The cases were consecutive ones except that of the earlier records those were excluded in which the history and findings described did not justify the diagnosis recorded. A rough check showed that the exclusion of such records did not affect the final figures. A high percentage of the cases had repeated examinations and electrocardiographic and x-ray studies. The

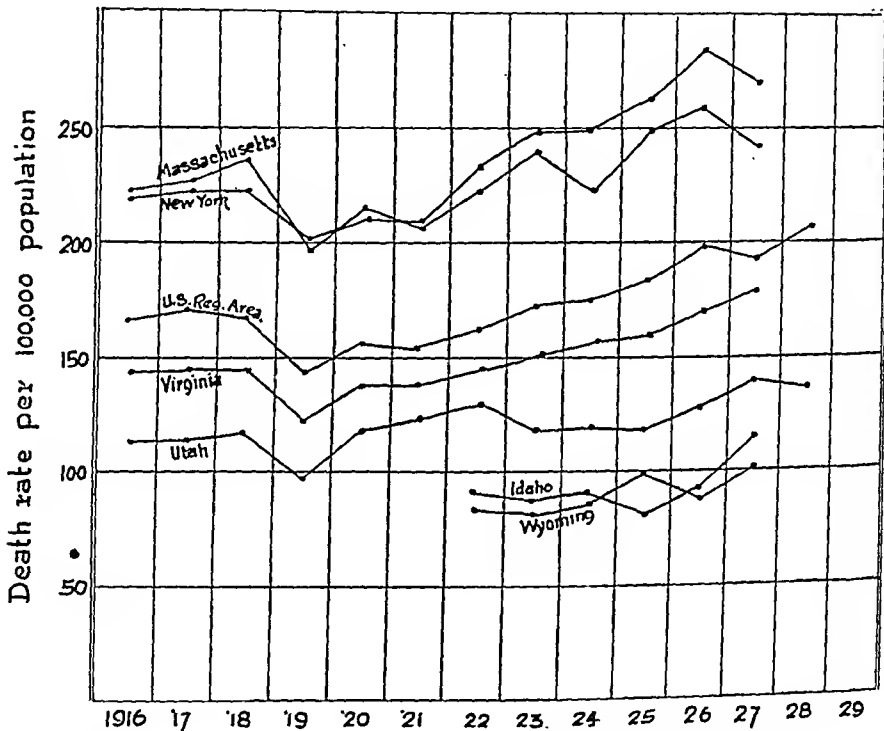


Fig. 3.—Heart disease death rates of certain states, 1916 to 1927.

cases represent consultant practice, ordinary private practice in home and hospitals, charity service at the Latter-Day-Saint Hospital in Salt Lake City and cases in the teaching of medical students at the Salt Lake County Hospital. As Salt Lake City is the medical center for Utah, southern Idaho, southern Wyoming and eastern Nevada a fair percentage of the cases were residents of Utah (88.5 per cent). Nearly one-half were residents of rural districts (Fig. 4) which corresponds fairly closely to the distribution of the population between urban and rural districts. These considerations, together with a comparison with some hospital statistics to be referred to later, seem to show that the series is truly representative of cardiac disease in this section.

[illegible]

Fig. 1.—One thousand cardiac cases.

The series included 867 cases of organic heart disease and 133 cases of irritable heart or cardiac neurosis. Cases with only sinus arrhythmia or functional murmurs were not included unless a diagnosis of cardiac neurosis or irritable heart was justified by history or other findings. Angina pectoris was not listed as a separate classification. Most of the cases presenting true angina were included under either the arteriosclerotic, hypersensitive, syphilitic or rheumatic groups. The others largely fell into the classification of unknown etiology. The same treatment was accorded auricular fibrillation as a diagnosis. A number of cases were due to more than one etiologic factor (Fig. 4).

The structural defects found, certain changes in mechanism, and the number of each type showing failure are shown in Fig. 4, but no discussion of these considerations will be presented.

In order that proper comparison may be made with similar series of cases reported from other sections of the country, only the cases of organic heart disease are included, and in view of the dual etiology of many cases each etiologic factor has been considered as an entity. For the series this gave 867 cases with 922 etiologic factors. Making a similar change in the figures of some other reports, a comparison, limited somewhat by differences in classification, was possible between the present series of cases and those reported by a few other writers (Table I).

TABLE I

| | VIRGINIA ⁸ | TEXAS ⁹ | NEW YORK CITY ¹⁰ | NEW ENG. ¹¹ | ROCKY MOUNTAINS |
|---------------------|-----------------------|--------------------|-----------------------------|------------------------|-----------------|
| No. cases | 300 | 915 | 1000 | 2421 | 867 |
| No. etiol. factors | 423 | 915 | 1051 | 3259 | 922 |
| Rheumatic | 15.6% | 7.3% | 42.7% | 29.3% | 44.0% |
| Arteriosclerotic | 32.4 | 13.7 | 22.3 | 26.3 | 21.1 |
| Hypertensive | 32.6 | 47.7 | | 21.7 | 14.9 |
| Syphilitic | 7.8 | 19.3 | 8.6 | 2.7 | 1.1 |
| Thyroid | 2.6 | 1.3 | | 2.1 | 9.3 |
| Angina pectoris | 6.6 | 2.3 | | 10.9 | |
| Congenital | .7 | .7 | | 1.1 | 1.1 |
| Unknown | 1.6 | | 17.8 | 2.2 | 7.3 |
| Subac. bact. endoc. | | 1.5 | | 1.4 | .2 |
| Miscellaneous | | 1.3 | 8.6 | 1.6 | .9 |
| Unclassified | | 4.9 | | | |

From Table I it is evident that the proportion of rheumatic cases is high in the Rocky Mountain region in comparison with the other sections considered. As remarked previously in the discussion of mortality statistics, the proportion of the living population under the age of forty-five years is high in this Rocky Mountain area. This may in part account for the high rheumatic figure, yet Texas and Virginia with their low incidence of rheumatic heart disease have age distributions of the population very similar to that of Utah, Idaho and Wyoming.

That thyroid heart disease is relatively more frequent in the Rocky Mountain section is not surprising as this is an endemic goiter area.

The low incidence of the syphilitic type is of interest. That the figure given is not due to error in diagnosis seems to be shown by a comparison of the mortality from syphilis and from aneurysm in the Rocky Mountain states and in other states. In Utah, Idaho and Wyoming the death rates from each are well below that of the registration area. This may be partly explained on the small colored population. A further check on the accuracy of the incidence of syphilitic heart disease will be referred to later in connection with some hospital statistics.

The age distribution of the different etiologic types (Fig. 4) was quite similar to that reported by Wyckoff and Lingg.¹⁰ The data available did not permit conclusions regarding the relative length of life at high and low altitudes. Such information would be desirable.

A comparison of the etiology of heart disease in the urban and rural portions of the series of cases was of interest (Table II).

TABLE II
ETIOLOGY OF HEART DISEASE IN URBAN AND RURAL PATIENTS

| | RHEUMATIC | ARTERIOSCLEROTIC | HYPERTENSION | SYPHILITIC | THYROID | CONGENITAL | UNKNOWN | SUBACUTE BACTERIAL ENDOCARDITIS | MISCELLANEOUS |
|-------------|--------------|------------------|--------------|------------|------------|------------|------------|---------------------------------|---------------|
| Urban (496) | 409 49.4% | 194 20.8% | 137 13.1% | 10 1.0% | 85 6.0% | 10 1.2% | 67 7.0% | 2 .4% | 8 .8% |
| Rural (412) | 39.3% | 20.6% | 17.0% | .9% | 13.1% | .9% | 7.4% | | .9% |

Only the rheumatic, arteriosclerotic and hypertensive groups are in number large enough to merit such comparison. There is a suggestively larger percentage of the rheumatic type in the urban patients. But no consideration has been given to changing residence.

The sixty-seven cases listed as "etiology unknown" raise many questions regarding possible causes of heart disease. Table III shows the possible etiology of these cases. Fourteen were probably due to one of the common etiologic factors, but as these were not clearly established it was thought best still to consider them of unknown etiology. Many of the others occurred in association with or following acute or chronic infections, but to state that they were certainly due to such infections would expose one to the *post hoc propter hoc* fallacy. The possibility of such error is best exemplified in the nine cases whose supposed onset followed influenza. None of these had had a complete examination (including electrocardiogram and x-ray) prior to the influenza; only such study would exclude the possibility that the influenza had merely served to bring a latent heart disease to consciousness.

TABLE III

HEART DISEASE OF UNKNOWN ETIOLOGY, SIXTY-SEVEN CASES

| | | | |
|---|---|-----------------------|----|
| 1. Probably one of recognized etiologic groups | | | 14 |
| Rheumatic | 3 | Syphilitic | 1 |
| Thyroid | 3 | Acute bacterial | 1 |
| Arteriosclerotic | 3 | Congenital | 1 |
| Hypertensive | 2 | | |
| 2. Possibly secondary to acute infectious disease | | | 11 |
| Influenza | 9 | Puerperal sepsis | 1 |
| Typhoid | 1 | | |
| 3. Probably secondary to pulmonary disease | | | 11 |
| Pneumonia | 6 | Tuberculosis | 2 |
| Asthma | 2 | Pneumonokoniosis | 1 |
| 4. Possibly secondary to chronic infections | | | 5 |
| Chronic sinusitis | 3 | Chronic cholecystitis | 2 |
| 5. Possibly toxic | | | 2 |
| Nephritic | 1 | Tobacco | 1 |
| 6. In association with obesity | | | 4 |
| 7. No cause apparent | | | 20 |

Some Hospital Statistics.—Hospital statistics on the incidence of heart disease have little value because of the general lack of uniformity in diagnostic criteria. They are presented here to serve as a rough check on the 1000 other cases discussed.

The Latter-Day-Saint Hospital in Salt Lake City is the largest hospital in the three Rocky Mountain states. Its admissions come from all three states. During the three years 1927, 1928 and 1929 there were 16,519 admissions of which 477, or 2.9 per cent, had a diagnosis of a heart disease or disorder. The numerous and various cardiac diagnoses were considered from an etiologic standpoint and duplication was eliminated. Such diagnoses as mitral stenosis, chronic endocarditis, valvular heart disease, etc., were considered as probably rheumatic. Where no etiologic factor was apparent from the diagnosis, the cases were listed as cause unknown or unspecified. In this manner 525 etiologic factors in the 477 cases were tabulated and a comparison was made with my own series. Cardiac neurosis and irritable heart were included in each instance.

TABLE IV

COMPARISON OF AUTHOR'S AND HOSPITAL SERIES

| | HYPER. RHEU. ART. "CHR. MYOC." | SYPH. | CONG. | THYR. | CARD. | NEUR. | UNK. | MISC. |
|------------------------|--------------------------------------|-------|-------|-------|-------|-------|------|-------|
| Author's series | 38.8% | 31.3% | .9% | .9% | 8.0% | 12.6% | 6.3% | .9% |
| 1000 cases | | | | | | | | |
| 1055 etiologic factors | | | | | | | | |
| Hospital series | 40.4% | 40.6% | 1.7% | 1.7% | 3.4% | .4% | 8.4% | 3.5% |
| 477 cases | | | | | | | | |
| 525 etiologic factors | | | | | | | | |

In view of the difficulty of evaluating the etiology of the hospital series the agreement seems close enough to serve as a check on my series.

COMMENT

Mortality statistics of heart disease in three of the Rocky Mountain states are presented. In contrast with other states they show relatively low rates. It is suggested that this lower mortality may be more the result of differences in age distribution of the population and a low percentage of urban life than of geographic or climatic conditions. Is it possible that the rising cardiac mortality throughout the United States is also partly the expression of the shift of the population from rural to urban life? It seems that the adjusted mortality in the lower age group does not show the wide state variation that the total mortality shows. Comment is made regarding the relatively high mortality in the lower age group in such southern states as Louisiana and Florida.

In studying 1000 cases of heart disease occurring in the Rocky Mountain states in comparison with other states the incidence of rheumatic heart disease seemed relatively high; it is again suggested that this may be partly due to the age distribution of the population. The thyroid heart disease incidence is high in contrast to other sections. The incidence of syphilitic heart disease is low, possibly at least partly due to the small colored population. The incidence of rheumatic heart disease seemed significantly higher in urban than in rural patients.

Reference is made to possible etiologic factors in the groups whose cause is listed as unknown.

Some hospital statistics are reported to serve as a check on my series.

No peculiarities in the etiology of heart disease were found that could be ascribed to the unique geographic or climatic conditions of this region except the high rheumatic and thyroid incidence.

REFERENCES

1. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *AM. HEART J.*, 3: 302, 1928.
2. Mortality Statistics, U. S. Census Bureau, 1923.
3. World Almanac, 1929.
4. Statistical Abstracts of the United States, 1929, Government Printing Office.
5. Whitney, Jessamine S.: Heart Disease Mortality Statistics, American Heart Association, May, 1927.
6. Mortality Statistics, 1927, U. S. Census Bureau.
7. Criteria for the Classification and Diagnosis of Heart Disease, Paul B. Hoeber, 1928.
8. Wood, J. E., Jones, T. S., and Kimbrough, R. D.: *Am. J. M. Sc.*, 172: 185, 1926.
9. Stone, C. T., and Vanzant, F. R.: *J. A. M. A.*, 87: 1, 1927.
10. Wyckoff, J., and Lingg, C.: *AM. HEART J.* 1: 446, 1926.
11. White, P. D., and Jones, T. D., *AM. HEART J.* 3: 302, 1928.
12. Statistical Abstracts of the United States, 1927, Government Printing Office.

ANEURYSM OF THE THORACIC AORTA

REPORT OF A CASE PRESENTING SOME UNUSUAL FEATURES*

EDWARD C. REIFENSTEIN, M.D., AND ELLERY G. ALLEN, M.D.
SYRACUSE, N. Y.

ALTHOUGH the literature contains accounts of many interesting and unusual syphilitic aneurysms, the case recorded in this paper seemed worthy of consideration, since it presented interesting and unusual clinical and pathological features, all of which are rarely to be noted in a single patient.

CASE REPORT

A fifty-seven year old, white, widowed salesman was admitted to the University Hospital on October 21, 1928, complaining of a swelling of seven years' duration over the upper, right anterior chest.

Family History.—The family history was of no significance. He was married thirty-three years before and had one child living and well. His wife died five years before; the cause of her death was not determined.

Past History.—His general health had been good. During childhood he had measles, mumps, scarlet fever and whooping cough. Thirty-five years ago he had a discharge from the urethra. Four years later there were symptoms of urethral obstruction which were relieved by treatment. He denied having had a penile lesion or any secondary manifestations of syphilis.

Present Illness.—The patient was in good health until seven years before when he noticed a mild, burning pain in the region of the right shoulder and over the right, upper, anterior chest. The pain was not related to exercise, excitement or the taking of food; its intensity, greater at some times than at others, was decreased by assuming various positions in bed. There was no definite position, however, that would always relieve the distress. The sensation was almost continuous for a period of eight weeks and at the end of that time there appeared in the region of the right nipple a small, nontender swelling, the size of an English walnut. A physician sent him to a hospital and on September 21, 1921, a roentgenogram of the chest was made† (Fig. 1). The x-ray diagnosis was aneurysm of the aorta. During the following six years he had occasional attacks of the burning previously described, coming on every three or four weeks and lasting not more than two or three days.

For the past year the pain had been more severe and intense, but had not been continuous. During this period the pain started in the region of the right nipple and frequently radiated down the right arm as far as the elbow. Occasionally he was relieved by shifting his position in bed, although he was not sure that one particular position was more effective in relieving the distress. The swelling on the

*From the Medical Service of the University Hospital, College of Medicine, Syracuse University, Syracuse, N. Y.

†We are indebted to Dr. C. F. Potter, Roentgenologist to the Crouse-Irving Hospital, for permission to reproduce this film.

chest increased only slightly in size until about six months before when it was found to be the size of a hen's egg. One month before it had increased to the size of a large apple, and the patient claimed that the tumor has doubled in size in the past two weeks. Two months before he consulted the Syracuse Free Dispensary. Potassium iodide was prescribed, the first antisyphilitic treatment he had received.

Other symptoms were: general weakness and gradual loss of weight during the past six years; slight twitching of the right hand associated with the attacks of chest pain for three months; marked dyspnea whenever the chest pain was severe; a moderate amount of cough with an occasional streak of blood in the sputum for five or six weeks.

Physical Examination.—The patient was a well developed, rather poorly nourished white man of fifty-seven years, sitting up in bed, breathing quietly, apparently in no acute distress. His mouth temperature was 98°, radial pulse 80 beats per minute, respirations 19 per minute. The left radial pulse had more volume than the right.



Fig. 1.—Roentgenogram of the chest made on September 21, 1921, which reveals aneurysm of ascending aorta.



Fig. 2.—Roentgenogram of the chest made on November 22, 1928, which reveals an area of increased density occupying the middle right lung field. The shadow of the ascending aorta cannot be separated from this area of density.

The blood pressure on each arm was 102/66 mm. Slight cyanosis of the lips and pallor of the skin were noted. The right pupil was larger than the left and reacted less readily to light, both pupils, however, reacting sluggishly to the reflex.

Over the right, upper anterior chest was a slightly tender, pulsating, expansile tumor, the size of a large grapefruit. The measurements of the mass were taken in the following manner: V (vertical), measured from the right midclavicular point to the lowest point of the tumor; T (transverse) measurements were taken from the midsternal line to the farthest lateral point; E (elevation), the elevation measured above the level of the sternum.

The vertical measurement was 17 cm.

The transverse measurement was 15 cm.

The elevation measurement was 5 cm.

At the upper medial aspect of the pulsating mass was a softer, and more tender, fluctuating portion which was more elevated than the surrounding area. The left border of cardiac dullness was 13.75 cm. from the midsternal line in the fifth

interspace. The apex impulse was not seen or felt. The heart sounds were of good quality, apex rate 80 beats per minute and regular. There was a loud, blowing systolic murmur heard over the precordium, with the maximum intensity noted at the apex. There was no abnormality of the second sound. The heart sounds and the systolic murmur could be heard over the pulsating mass.

Examination of the lungs revealed a few moist râles at the left base posteriorly. There was clubbing of the fingers with moderate cyanosis of the nail beds. The deep reflexes were equal and active.

Laboratory Studies.—Red blood count, 4,800,000; hemoglobin, 60 per cent (Sahli); white blood count, urine, blood chemistry and renal function were normal. Complement-fixation test for syphilis: The fixation of complement was complete with the cholesterinized and the noncholesterinized antigens.

A fluoroscopic examination of the chest revealed "a pulsating mass, the size of a grapefruit, in the anterior portion of the mid right lung field, apparently arising from the ascending aorta." A roentgenogram of the chest showed a round shadow. The trachea and heart were displaced to the left (Fig. 2).

Clinical Course and Progress.—The mass gradually increased in size, and the pain became so severe and intense that for the greater part of the time opiates were required. Two months after admission the measurements of the tumor were: (V) 22 cm.; (T) 16 cm.; (E) 8 cm. It was noted that the skin over the mass in the region of the nipple was blanched with a small area of ecchymosis surrounding it.

On January 24, 1929, three months after admission, the measurements of the tumor were: (V) 26 cm.; (T) 25 cm.; (E) 11 cm. The circumference of the tumor around its base on the chest wall was 70 cm. The patient was very weak. The blood pressure reading on the right arm was 104/74 mm., on the left 118/88 mm. There was dullness at the right base posteriorly, and the breath sounds over this area were considerably diminished. Marked dyspnea was present. The radial pulses were of poor quality but synchronous. The right radial pulse was almost imperceptible. The patient grew weaker, and on the morning of February 9 it was noted that he had marked inspiratory dyspnea. On February 10, 1929, the patient died.

*Necropsy.**—"Body is that of a fairly well developed, poorly nourished adult male, 171 cm. in length. There is a large, rather irregular mass on the anterior surface of the right chest wall. This mass is soft and fluctuating and measures 65 cm. around its base, 20 cm. in diameter in one direction, 22 cm. in diameter in the other direction and 11 cm. in height. The skin is pulled tightly over this mass and is adherent to it.

"On opening the body the usual midline incision is made from the upper part of the sternum to the symphysis, exposing the peritoneal cavity. On the left side the muscles and skin are reflected from the chest wall as usual. On the right side the skin is reflected from over the mass by making an incision below the mass at about the level of the costal margin, extending from the midline incision upward and backward to about the mid-axillary line. The skin is then reflected." The peritoneum is without evident lesion.

"On opening the chest wall on the left side as usual, the ribs are cut through at the junction of the cartilages. On the right side the ribs are cut through just beneath the skin and soft tissues. The line of incision is carried upward and backward to the intercostal space between the 2nd and 3rd ribs and then the intercostal muscles in this space are cut up to the clavicle. The pleural cavities are

*This is a partial report of the complete autopsy performed on February 11, 1929, by Dr. H. G. Weiskotten, Dean of the College of Medicine.

examined and then the viscera removed in one mass. The organs are then dissected away and examined, leaving the aorta, heart and pericardial cavity in relation to one another.

"Pleural Cavities: The right pleural cavity contains about 300 c.c. of a clear amber-colored fluid. There is no free fluid in the left cavity. Pleural surface of both lungs is fairly smooth and glistening. The right lung is somewhat collapsed, the mass and fluid occupying almost the entire right pleural cavity.

"Lungs: Weight not unusual. Surface of both lungs is somewhat reddish in color and smooth and glistening. On section the cut surface is not unusual. On pressure there can be expressed a moderate amount of reddish and grayish frothy fluid."

Spleen, liver, gall bladder and ducts, pancreas, kidneys, adrenals, and organs of the pelvis were not remarkable.

"Mass, Heart and Aorta: After removing the above described organs, the heart and aorta, which are left attached together, are examined. The aorta is opened throughout its entire length, beginning in the abdominal aorta and extending into the left ventricle. When this is done it is found that the mass is in direct

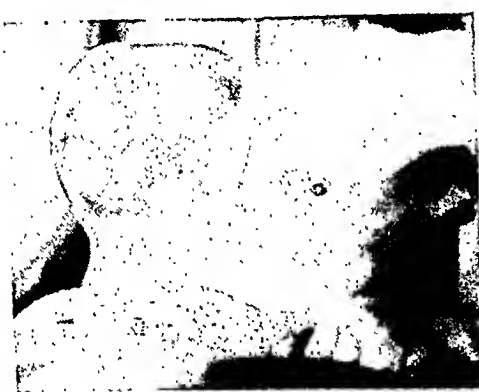


Fig. 3.—Appearance of aneurysm, illustrating size and elevation.



Fig. 4.—Note relative size of aneurysm and chest wall.

continuity with the first portion of the aorta 6 cm. above the heart, there being an opening between the mass and the aorta at this point, measuring about 3 x 4 cm., across, allowing the blood free circulation into the mass. Between this opening and the heart there was another small pouching of the aorta, measuring about 3 cm. across and about 2 cm. in depth. A portion of the wall of the mass is removed, beginning at the aorta and extending down one side of the mass, clearly demonstrating that there is a communication between the aorta and the mass. Most of the lumen of this mass is filled with organized blood clot, but the center is composed of fluid blood and post-mortem blood clot. On further examination it is found that the mass had eroded through the ribs and had extended to the external surface. The entire specimen was preserved and there was no further examination of the heart or pericardial cavity.

"Anatomical Diagnosis.—Aortitis; Aneurysm of the first portion of the aorta; edema and congestion of the lungs; some acute nephritis; right sided hydrothorax with collapse of the lung; marked generalized arteriosclerosis."

COMMENT

The particular features of interest in this case seemed to be the size of the lesion, its duration and the termination.

Size.—Rarely are aneurysms seen that have reached such a tremendous size as the one described. Osler¹ states that “when perforation of the chest occurs, the size of the adult head may be reached, and with its contents the aneurysm may weigh five or six pounds. Broadbent² declares that “aneurysm of the ascending aorta may attain very great size, sometimes being as large as a child’s head.” Figs. 3 and 4 show the tumor protruding through the anterior chest wall. Fig. 5 shows the post-mortem specimen, illustrating the relative size of the aneurys-



Fig. 5.—Note the relative size of the aneurysmal tumor (A) and the heart (B), also the aorta cusps (C) and the aorta (D).

mal tumor and the heart of normal size. It will be recalled that two weeks before death the tumor on the anterior chest wall measured 70 cm. in circumference and protruded 11 cm. in front of the sternum.

Duration.—A most unusual feature of this case was its duration. Colt³ found the average clinical duration in 101 cases to be 19.6 months. Lemann's⁴ series of 84 cases includes no case of more than 48 months. Broadbent² states: “When situated in the ascending portion of the arch above the pericardium, the patient may live for some years without experiencing much inconvenience from it, especially if the aneu-

rysm extends forward and makes its way through the chest wall." Cabot⁵ believes that when symptoms finally appear they usually lead to death within two years. Sailer⁶ reported a patient who lived for three and one-half years after wiring and then died of unwarranted exertion. In the case presented we have definite knowledge of the existence of the aneurysm for at least seven years. A further point of interest is that it was not until the aneurysm had made its external appearance on the anterior chest wall that the patient was examined and the nature of his lesion determined. The roentgen-ray appearance of the aneurysm in September, 1921, is shown in Fig. 1. The roentgenogram of the chest in November, 1928, is illustrated in Fig. 2. For six and one-half years the size of the external tumor remained practically stationary, according to the history given by the patient.

Termination.—When one considers the size and duration of the tumor, it seems remarkable that there was no point of rupture, either externally or internally. When rupture occurs, it is more likely to be internal. However, one could hardly fail to have been impressed by the thinness of the stretched skin over the large, protruding, pulsating mass. Those who examined the mass after it had reached this tremendous size were indeed reluctant to palpate the lesion lest the slightest pressure precipitate what seemed almost inevitable.

There is general agreement^{5, 7, 8, 9, 10, 11} in the view that whereas from one-fourth to one-half of all cases of aneurysm terminate in rupture it is very rare to have the rupture occur externally. In the case described in the present communication it has been pointed out that there were no clinical signs or symptoms of rupture; the post-mortem examination also failed to reveal any point of rupture.

SUMMARY

A case of thoracic aneurysm presenting some unusual features is reported. Previous to death the protruding aneurysmal tumor measured 70 cm. around its base and was elevated 11 cm. above the level of the sternum, illustrating the fact that aneurysms of the thoracic aorta may reach a size larger than is generally appreciated. Evidence is presented to show that the aneurysm was present for more than seven years. Clinical and post-mortem examinations failed to reveal any point of rupture in the aneurysmal wall. The fact that this type of termination may occur in an aneurysm of unusual size and duration should be appreciated by the physician when considering prognosis.

REFERENCES

1. Osler, Wm.: *Modern Medicine* 4: 458, 1908.
2. Broadbent, Wm. H.: *Heart Disease*, New York, 1906, pp. 455 and 471, William Wood & Company.
3. Colt, G. H.: *Clinical Duration of Saccular Aortic Aneurysms in British Born Subjects*, *Quart. J. Med.* 20: 331, 1927.

4. Lemann, I. I.: Aneurysm of the Thoracic Aorta, Its Incidence, Diagnosis and Progress. A Statistical Study, *Am. J. M. Sc.* 152: 210, 1916.
5. Cabot, R.: Facts on the Heart, Philadelphia, 1926, pp. 336 and 369, W. B. Saunders Co.
6. Sailer, J.: Diagnosis of Aortic Aneurysm, *M. Clin. N. Amer.* 10: 1479, 1927.
7. Boyd, L. J.: A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta, *Am. J. M. Sc.* 168: 654, 1924.
8. Clawson, B. J., and Bell, E. T.: The Heart in Syphilitic Aortitis, *Arch. Path. & Lab. Med.* 4: 922, 1927.
9. Warfield, L. M.: Tice System of Medicine 6: 31, 1928.
10. Norris, G. W.: Syphilitic Aortitis, *M. Clin. N. Amer.* 3: 1387, 1920.
11. Norris, G. W., and Fetterolf, G.: Frozen Sections From a Case of Protruding Aneurysm of the Arch of the Aorta, *Arch. Int. Med.* 26: 114, 1920.

Department of Clinical Reports

ARTERIOVENOUS ANEURYSM BETWEEN AORTA AND SUPERIOR VENA CAVA. CASE REPORT*

MAURICE PACKARD, M.D., AND H. F. WECHSLER, M.D.,
NEW YORK, N. Y.

SINCE 1832 when Beever¹ described the first example of arteriovenous aneurysm between aorta and vena cava, about sixty cases have been reported in the literature. The first correct clinical diagnosis was apparently made by Mayne² in 1853. Pepper and Griffith³ were the pioneers in this country to direct attention to this interesting and unusual condition. In 1890 they were able to collect and analyze forty-three cases, establishing the diagnostic criteria for its clinical recognition. Except for the incomplete surveys of the literature by Fussell⁴ and by Herriek,⁵ very little has been added to our knowledge of the subject since that time. We have been fortunate to observe and autopsy a typical example of this condition, and because of its rarity we are publishing the case.

CASE REPORT

A. L., a Pole, thirty-eight years of age, a truckman by occupation, was admitted to the Gouverneur Hospital August 30, 1929, complaining of headache, dizziness and difficulty in breathing.

His past history was entirely negative and he denied venereal disease by name and symptoms. He had been performing his usual strenuous work in his capacity as a truckman when with absolutely no prodromal symptoms he was suddenly seized with intense headache and dizziness. Associated with these were a choking sensation, great difficulty in breathing and a frequent distressing cough. His face and neck had at the same instant become markedly swollen and deep blue in color. He had vomited once before his admission.

On physical examination, he presented a striking and unique appearance. The outstanding feature was the peculiar disproportion between the upper and lower halves of his body. His face, neck, upper extremities and the upper half of his chest were not only greatly swollen and pitted on pressure but were extremely cold and cyanotic. The upper extremities were least involved and both the edema and cyanosis stopped abruptly at the level of the fourth rib. He was markedly dyspneic and orthopneic and visibly in great distress. The conjunctivae were greatly congested. The pupils, though regular in outline, reacted sluggishly to light and in accommodation. The mucous membranes of his nose and mouth were cyanotic, as were his ears. His neck could only be described as bull-like in character, and, although the veins were engorged, no pulsation could be discovered. His chest was difficult

*From the Medical Service of the Gouverneur Hospital.

to examine because of the edema. The apex impulse of the heart was located in the seventh left interspace in the midaxillary line. The heart was also enlarged to the right. The manubrial dullness was increased, especially beneath the right clavicle, but the exact extent was difficult to determine. A systolic thrill was palpable at the base, and a very loud murmur was heard over the entire chest, louder, however, over the aortic region. The murmur was of a peculiar character. It was continuous through both systole and diastole, but became markedly intensified with each systolic contraction. It was high pitched and slurring in quality, and completely replaced the first sound. The second sound was inaudible. The pulse was of the Corrigan type, and the blood pressure in each arm was as follows: right, 190/0 mm.; left, 176/20 mm. Moist râles were heard over both bases of the lungs.

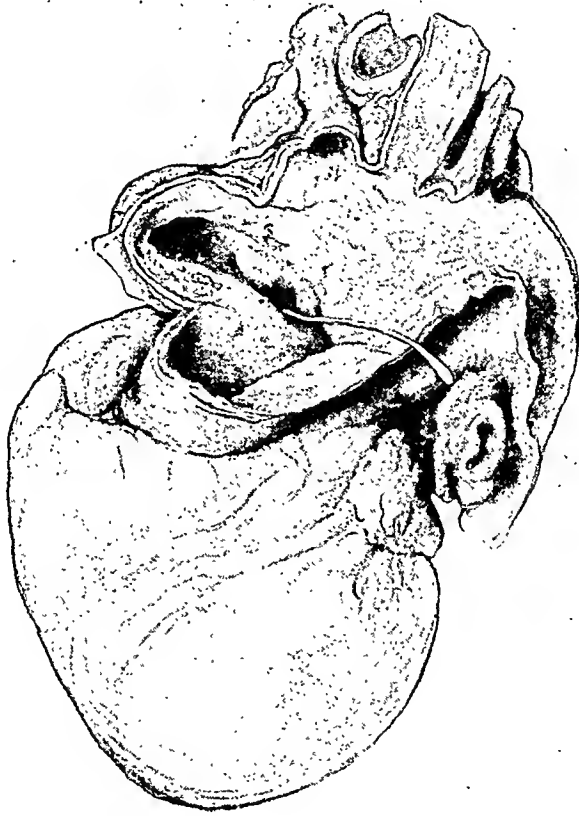


Fig. 1.—Arteriovenous aneurysm, anterior view.

The liver and spleen were not palpable. The lower extremities exhibited no abnormalities and were in marked contrast to the upper. The reflexes were normal and no pathological reflexes were present.

The laboratory findings were as follows: Urine: albumen 1 plus; a few hyaline casts. Blood count: R.B.C. 7,400,000; W.B.C. 17,200; polynuclear cells 63; lymphocytes 31; mononuclears 6. Wassermann: 3 plus. Blood Chemistry: N.P.N. 128; sugar 105.

The clinical course was extremely brief. He gradually became increasingly sleepy, finally lapsed into coma, and died twelve hours after his admission and fourteen hours after the onset of his illness.

The autopsy findings as they relate to the heart and vessels are as follows (Figs. 1 and 2): The pericardial sac contains no excess of fluid and is free of

adhesions. The heart is moderately enlarged, measuring 11.8 cm. x 12.2 cm. x 5 cm. Together with the great vessels, it weighs 660 gm. The epicardial fat is diminished in amount, and on the anterior surface of the left ventricle near the apex is a tendinous fleck about 1 cm. in circumference. The left ventricle is slightly dilated and moderately hypertrophied, its wall measuring 1.8 cm. to 2.2 cm. in thickness. The right ventricle is moderately dilated and hypertrophied, its wall measuring 0.5 cm. to 0.7 cm. in thickness. The right auricle is markedly dilated and filled with ante-mortem thrombi. The valves are negative except for a dilatation of the tricuspid ring and slight thickening of the corpora arantii of the aortic cusps. The heart muscle is yellowish-brown in color and somewhat friable.

Arising from the aortic arch by a wide mouth, is a sacular aneurysm, the size of an orange. The sacculatation commences 3 cm. above the aortic ring and extends



Fig. 2.—Arteriovenous aneurysm, posterior view.

to the right and posteriorly. From the base of the aneurysm, there projects a shallow secondary sac, the size of a walnut. Its wall is very thin and translucent and exhibits, approximately in its center, a circular perforation 0.4 cm. in diameter. The edge of the perforation is ragged and hemorrhagic and a probe passed through it enters the superior vena cava. The floor of the aneurysm proper is covered with reddish-gray thrombi. The intima of the thoracic aorta is greatly altered. It is cloudy, thrown into irregular folds and furrows and shows numerous hyaline, translucent, slightly raised nodules. The coronary arteries show some narrowing of their orifices and a few atheromatous plaques in the left anterior descending branch near its origin.

The superior vena cava is markedly dilated and intimately adherent to the aneurysm. The perforation is situated 2 cm. above the termination of the vein in the right auricle and 1.5 cm. above the opening of the vena azygos. It is slightly smaller than on its aortic aspect. The intima of the superior vena cava exhibits no other abnormalities.

Microscopically, the heart muscle shows hypertrophy, marked edema, slight interstitial fibrosis and moderate hyaline and fatty degeneration of the muscle fibers. The aorta is the seat of a typical luetic mesaortitis. Miliary gummata are present about the vasa vasorum, and the greatly scarred media are invaded by this cellular granulation tissue, which often surrounds necrotic foci. The intima is thickened and hyaline.

Sections near the perforation reveal the wall of the aneurysm to be composed of hyaline fibrous tissue, covered with a thin layer of hyalinized thrombus. The adventitia is profusely infiltrated with round and plasma cells and an occasional multinucleated giant cell. The wall of the vein is sparsely infiltrated with round and plasma cells. As the perforation is approached, both walls become increasingly edematous and more markedly infiltrated with inflammatory cells, mostly polynuclear cells. Large necrotic foci appear in the wall of the aneurysm surrounded by these inflammatory cells. Finally, at the site of perforation the walls are completely necrotic and densely infiltrated with polynuclear cells, many of the latter being in various stages of degeneration and disintegration. All the changes described are much more pronounced in the artery than in the vein.

COMMENT

We do not wish to enter into an elaborate discussion of the many interesting phases of this condition, but we cannot refrain from enumerating briefly the cardinal diagnostic criteria which this typical case demonstrates so well. They are:

1. Evidences of obstruction to the circulation of blood in the superior vena cava and its tributaries: cyanosis, edema, coldness and distention of the veins.
2. The suddenness of the onset of these symptoms.
3. Evidence of a tumor in the thorax and the probability that it is aneurysmal in nature.
4. The existence of a murmur characteristic of a communication between an artery and a vein, that is, a continuous one intensified by systole.

Not all these criteria are always present, and they may be greatly modified, but a typical case such as this not only offers no diagnostic difficulties but remains forever indelibly impressed on the memory.

REFERENCES

1. Beevor: *Lancet* 1: 800; 2: 63, 1832.
2. Mayne: *Dublin Quart. J. Med. Sc.*, p. 257, 1853.
3. Pepper and Griffith: *Tr. A. Am. Physicians* 5: 45, 1890.
4. Fussell: *Tr. A. Am. Physicians* 21: 142, 1906.
5. Herrick: *Am. J. M. Sc.* 158: 782, 1919.

TWO-TO-ONE RIGHT BUNDLE-BRANCH BLOCK

LUTHER W. KELLY, M.D.

CHARLOTTE, N. C.

TWO-TO-ONE right bundle-branch block is a rare phenomenon that has been reported only once.¹ It consists of a normal sino-auricular rhythm with the alternation of normal and abnormal ventricular complexes, the abnormal complex exhibiting right bundle-branch block.

In 1928 Leinbach and White published a report of their case which progressed to complete right bundle-branch block within a period of five days. The first electrocardiogram showed a pure two-to-one right bundle-branch block, the second showed the same phenomenon, but with contiguous blocked impulses occurring once; the third, complete block of the right bundle of His. Included in their report were tracings obtained by Dr. Stenstrom of Sweden in which this phenomenon occurred as a brief event of a few beats' duration between relatively normal bundle-branch conduction and complete right bundle-branch block. In the latter case exercise with increase in the heart rate impaired intraventricular conduction, while slowing of the rate by vagal pressure restored normal conduction.

Baker² has described a temporary bundle-branch block occurring during tachycardia, with restoration of normal intraventricular conduction as the heart rate became slower. The administration of oxygen raised the threshold for defective conduction so that the normal complexes persisted in spite of an increase in rate that previously had produced the block. Electrocardiograms have been published illustrating variations in degree of block or even alternating right and left bundle-branch block, but except for the two cases cited by Leinbach and White the two-to-one phenomenon has not been observed.

An additional case of two-to-one right bundle-branch block is reported here. The patient was referred for an electrocardiogram by Dr. Lucius G. Gage of Charlotte, when he noticed on physical examination a striking alternation of the first heart sounds, one being clear and ringing, the next soft and muffled. There was no accompanying alternation in blood pressure.

CASE REPORT

Mrs. F. W. White, a primipara, aged 61 years.

Diagnosis: (1) Hypertensive cardiovascular disease; (2) congestive failure; (3) right bundle-branch block.

Complaint: Dizziness, palpitation.

Family History: Father died at 86 years of age following a third cerebral hemorrhage; paternal grandfather died at 86; paternal grandmother at 80; mother died at 66 suddenly of unknown cause; one brother died at 50 of cerebral hemorrhage; two sisters died during operations; one brother and two sisters are living and well.

Previous Medical History: She does not remember any contagious diseases in childhood but did have malaria. She had typhoid fever at sixteen; pneumonia twice in adult life and a tonsillectomy at 57 years. In 1928 she had an illness characterized by tachycardia and vertigo lasting a few weeks. Her systolic blood pressure is reported to have been over 200 mm. of mercury and her pulse 120 at that time.

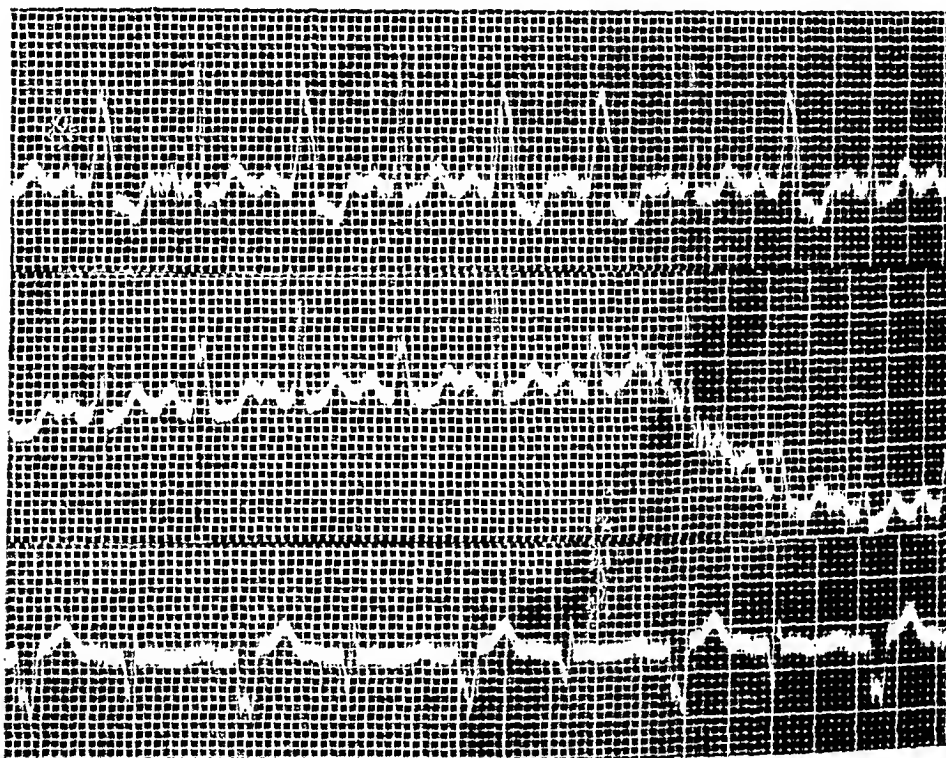


Fig. 1.—Electrocardiogram (Leads I, II, and III) taken April 14, 1930, showing a sinus rhythm, rate 140, and two-to-one right bundle-branch block. Two successive blocked impulses are seen in Lead I. This occurred again in Lead I (not shown) but did not occur elsewhere.

Present Illness: Her present symptoms appeared in the latter part of March, 1930, following an active social life with financial worries of several months' duration; in addition she had been under a mental strain most of her adult life due to marital difficulties. Her first symptoms were transient palpitation, tachycardia, and vertigo following emotional stress. These attacks became more frequent, of longer duration, and in addition she had edema of the ankles, dyspnea on exertion and slight orthopnea.

Physical Examination (April 14, 1930): Showed a well nourished woman of 61 years, mentally alert though apprehensive and irritable.

The eyes, ears, and nose were negative; the tongue was coated, and there was extensive pyorrhea alveolaris. The thyroid gland was not palpably enlarged; there was no exophthalmos or tremor, no enlargement of the cervical lymph nodes.

At the bases of both lungs there were numerous medium moist râles.

Heart: The heart was enlarged to the left, and the rate was rapid, but there were no murmurs. A definite alternation in the first sounds was heard and consisted of a clear ringing sound alternating with a softer muffled sound. This was heard with equal intensity over both the aortic and the pulmonic areas. The systolic blood pressure was 220 mm. of mercury, the diastolic 110 mm.; no alternation in the systolic or diastolic pressure to correspond with alternation in the heart sounds was heard.

The abdomen was pendulous but otherwise negative. The liver and spleen were not palpable.

The skin, the extremities except for slight edema of the ankles, and the reflexes were normal.

Laboratory Data: The urine was acid in reaction with a specific gravity of 1.010 and contained a faint trace of albumin but no sugar, and had no pus, blood,

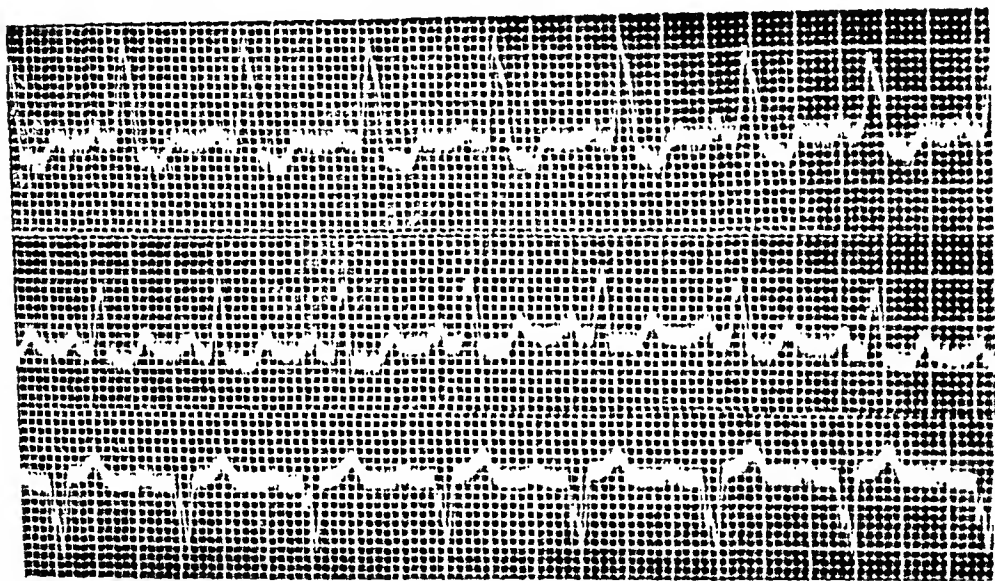


Fig. 2.—Electrocardiogram (Leads I, II, and III) taken April 17, 1930, showing a sinus rhythm and complete right bundle-branch block, rate 105.

or casts in the sediment. The white blood count was 9,900; the red cell count was 5,200,000; the hemoglobin 100 per cent. A few days later the blood sugar four hours after breakfast was 98 mg. per 100 c.c. of blood; the blood urea nitrogen 6.8 mg., the creatinin 1.27 mg. The Wassermann test was negative. Basal metabolism determinations were unsatisfactory, ranging from +8 per cent to +14 per cent, and she refused to attempt further tests.

Electrocardiograms: A tracing (Fig. 1) taken at the time of her first examination, April 14, 1930, shows a sinus rhythm, rate 140, and two-to-one right bundle-branch block save for two instances in Lead I where two successive blocked impulses are seen. A tracing (Fig. 2) taken April 17, 1930, after the patient had taken a total of 10.5 grains of powdered digitalis leaf during the preceding two days, shows a sinus rhythm, rate 105, and complete right bundle-branch block. A third tracing taken May 22, 1930, also shows a sinus rhythm with complete bundle-branch block. Symptomatically she had improved and had failed to return for more frequent observation as requested. Prior to this last tracing she had been taking 1.5 grains of digitalis daily but had voluntarily discontinued the drug four or five days previously.

SUMMARY

A case is reported showing at first two-to-one right bundle-branch block and later complete right bundle-branch block. Only two other instances of this phenomenon have been found in the literature, both being recorded in the same report; one of these was a brief transitional event, the other of longer duration to which the case reported here is comparable.

REFERENCES

1. Leinbach, R. F., and White, Paul D.: Two-to-One Right Bundle-Branch Block, *AM. HEART J.*, 3: 422, 1928.
2. Stenstrom, Nils: Contribution to the Knowledge of Incomplete Bundle-Branch Block in Man, *Acta med. Scandinav.*, 57: 385, 1922.
3. Stenstrom, Nils: An Experimental and Clinical Study of Incomplete Bundle-Branch Block, *Acta med. Scandinav.*, 60: 552, 1924.
4. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the Auriculo-Ventricular Bundle, *Arch. Int. Med.*, 13: 803, 1914.
5. Robinson, G. C.: Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch. Int. Med.*, 18: 830, 1916.
6. Willius, F. A., and Keith, Norman M.: Intermittent Incomplete Bundle-Branch Block, *AM. HEART J.*, 2: 255, 1927.
7. Mathewson, George D.: Lesions of the Branches of the Auriculo-Ventricular Bundle, *Heart*, 4: 385, 1912-13.
8. Baker, B. M.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle-Branch Block, *Arch. Int. Med.*, 45: 814, 1930.
9. Resnik, W. H.: Observations on the Effect of Anoxemia on the Heart, *J. Clin. Investigation*, 2: 125, 1925-26.

CONGENITAL HEART-BLOCK

REPORT OF A CASE

MEYER SCLAR, M.D.

BROOKLYN, N. Y.

IN DISCUSSING congenital heart-block Maude E. Abbott,¹ in her comprehensive study of "Congenital Cardiac Disease," states that "This is a rare condition, but of great interest from the physiological standpoint and from that of the cardiac anomaly which is nearly always associated." Abbott further states that of the cases reported in the literature, only those having been proved by graphic records and where the history of the block dates back to early childhood, can be considered as cases of congenital heart-block. Of such cases she states there were sixteen in the literature, only one of which, that of Wilson and Grant,² having come to autopsy.

The following year (1928) Davis and Stecher³ published twenty cases of congenital heart-block, nineteen from a review of the literature and one of their own, these cases having been proved by electrocardiograms or pulse tracings.

A year later, Yater⁴ working at the Mayo Foundation published thirty cases of proved congenital heart-block, twenty-nine from a review of the literature and one of his own. Of these thirty cases, three came to autopsy—that of Wilson and Grant² as already mentioned, that of Perotti⁵ and his own.

It is important to note that of the cases proved by graphic records, those studied with the electrocardiograph are undoubtedly the most convincing. When Fulton, Judson and Norris⁶ published a paper entitled "Congenital Heart-Block" occurring in a father and two children, one an infant, proving this condition with polygraphic tracings, White, Eustis and Kerr⁷ denied their contention, stating that only the infant's tracing showed a true block, whereas the other two polygraphs were normal, yet were not correctly interpreted.

As for the factors responsible for the production of congenital heart-block, it should be mentioned that, in those two of the three cases that came to necropsy, and in which histological studies were made, developmental defects in the auriculoventricular bundle were found and not a prenatal endomyocarditis.

CASE REPORT

History.—Bernard F., a boy, aged fourteen years and eight months old, was recommended to our cardiac clinic at the Crown Heights Hospital on January 14, 1930, by Dr. Louis R. Lang because of an abnormality of the heart, manifesting it-

self by a loud systolic murmur heard over the midprecordium and discovered by him during a casual examination. The boy himself had no symptoms referable to the heart. In fact he complained only of occasional frontal headaches coming on especially after school, not relieved by glasses. He had been a full-term baby, delivered spontaneously, weighed seven pounds at birth, was breast fed until seventeen months of age and never cyanotic. He sat up at six months and showed his first teeth at seven months. He began to walk between eighteen months and two years. His mother, who was both intelligent and cooperative, told us that as a youngster his appetite was very poor and he developed very slowly; at the age of eight years he weighed only 30 or 35 pounds.

This year he changed two of his deciduous teeth and he still has three deciduous teeth left. His past history is absolutely negative for rheumatic fever, chorea, diphtheria, tonsillitis or scarlet fever. He had measles and mumps when seven years of age. When he was four years old, his mother took him to the country. While there, he was taken to a physician because of a slight cold. The doctor at that time asked the mother if she knew there was something wrong with the boy's heart. At present his appetite is good, he sleeps well and his bowels are regular.



Fig. 1.—Teleroentgenogram. Enlargement of all cardiac diameters indicated by measurements.

He is alert mentally, being in the second year in high school. He was always excused from gymnasium exercise because of the murmur.

The family history is essentially negative, father and mother being well, as is a sister of twenty-two years of age. He lost recently, a brother of twenty-one, of some streptococcus infection—which prompted the mother to have this boy thoroughly examined.

Physical Examination.—The boy was 59 $\frac{3}{4}$ " tall and weighed 103 lb. His color was good. The fingers showed no cyanosis or clubbing. The pulse rate was 48 per minute, regular and full and corresponded with the apex rate. The apex impulse was in the fifth intercostal space, slightly outside the nipple line. No thrill was palpable anywhere over the precordium. The left border of the heart extended 8.5 centimeters in the fifth space to the left of the midsternal line and right border extended 4.75 centimeters to the right of the midsternal line. A loud systolic murmur was audible over the precordium with maximum intensity in the second and third interspaces, immediately to the left of the sternum. P-2 was slightly accentuated as compared with A-2.

Laboratory Observations.—The urine showed a faint trace of albumin, otherwise was negative. The blood count showed 4,130,000 red cells and 6,000 white cells.

Hemoglobin was 83 per cent (Sahli). A teleroentgenogram and fluoroscopic examination showed an enlarged heart increased in all diameters (Fig. 1) with a slight fullness in the pulmonic region and vigorous pulsations in the region of the pulmonic conus. The cardiothoracic ratio was 58, which is considerably above normal for his age and development. Wassermann reaction was negative and the blood chemistry was entirely normal. His blood pressure was 120 mm. systolic and 65 diastolic.

The electrocardiogram showed complete auriculoventricular dissociation, with tendency to right ventricular preponderance. The auricular rate was 83 per minute, and the ventricular rate was 48; both were regular (Fig. 2).

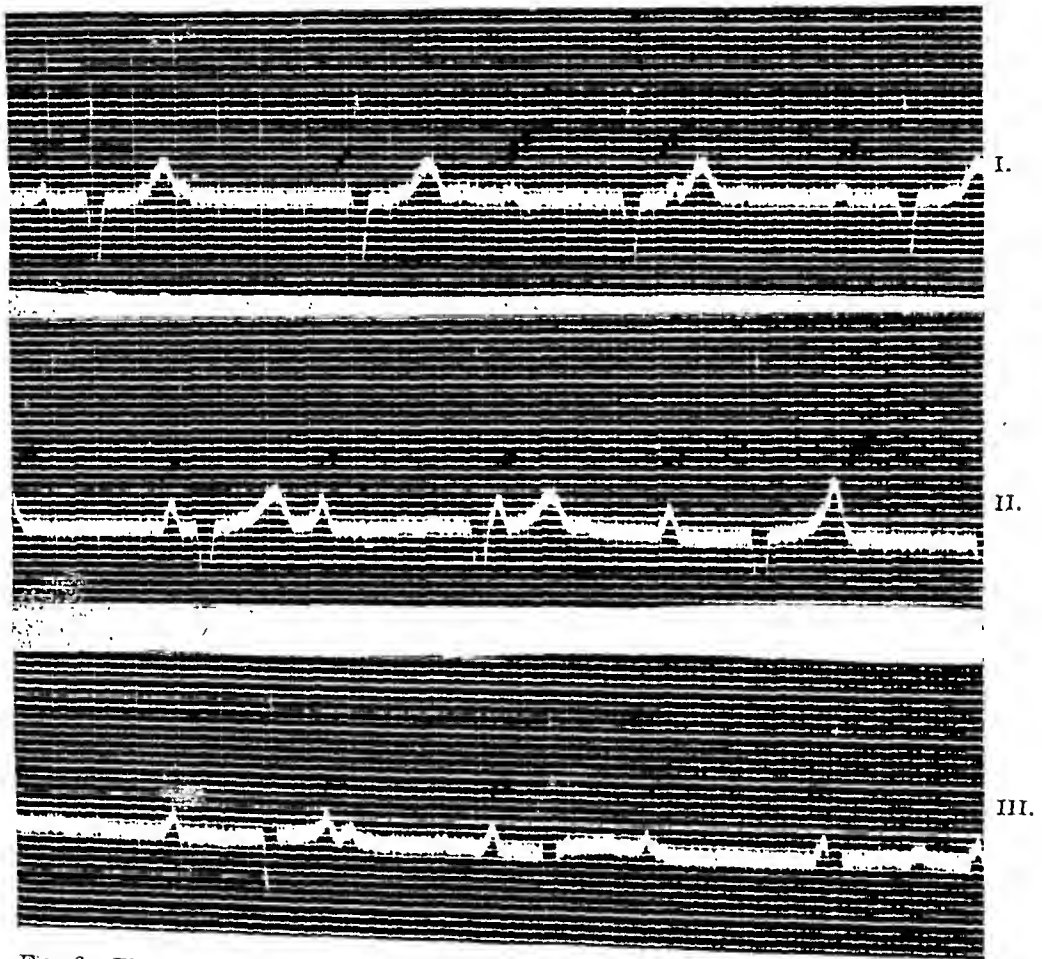


Fig. 2.—Electrocardiogram, Leads I, II, III. Complete auriculoventricular dissociation with tendency to right ventricular preponderance.

Clinical Course.—We reexamined him on February 1, 1930, and again on March 15, 1930, and on both occasions he showed a pulse rate under 50, exercise (jumping first on one foot and then on the other for three minutes) having no effect upon his pulse rate. His blood pressure on both occasions was 120 mm. systolic and 65 diastolic. He is still under our observation.

COMMENT

This case bears out previous observations by others, that cardiovascular symptoms, such as precordial pain, dyspnea, palpitation, syncope, cyanosis or clubbing of the extremities are conspicuous by their

absence, despite the complete heart-block. In fact the patient never complained and never had electrocardiograms taken before, although the mother knew he had a murmur and slow heart since early childhood. It was rather his brother's premature death that prompted this examination, with the result that the complete heart-block was incidentally discovered.

Developmental defects usually occur in multiples. In this case heart-block, probably resulting from developmental defect of the bundle, was associated with the retention of the deciduous teeth to a late age.

REFERENCES

1. Abbott, Maude E.: Congenital Heart Disease, Osler's Modern Medicine, Lea & Febiger 4: 667, 1927.
2. Wilson, J. G., and Grant, R. T.: A Case of Congenital Malformation of the Heart in an Infant Associated with Partial Heart Block, *Heart* 12: 295, 1925-1926.
3. Davis, Hart, and Stecher, Robert M.: Congenital Heart Block, *Am. J. Dis. Child.* 36: 115, 1928.
4. Yater, Wallace M.: Congenital Heart-Block, *Am. J. Dis. Child.* 38: 112, 1929.
5. Perotti, D.: Blocco cardiaco congenito con vizio di conformazione del cuore, *Boll. d. Soc. med.-chir. di Pavia* 3: 1, 1928.
6. Fulton, Z. M. K., Judson, C. F., and Norris, G. W.: Congenital Heart-Block Occurring in a Father and Two Children, One an Infant, *Am. J. M. Sc.* 140: 339, 1910.
7. White, P. D., Eustis, R. S., and Kerr, W. J.: Congenital Heart-Block, *Am. J. Dis. Child.* 22: 299, 1921.

Department of Reviews and Abstracts

Selected Abstracts

Cookson, Harold: The Etiology and Prognosis of Auricular Fibrillation. *Quart. J. Med.* 23: 309, 1930.

The prognosis in the two largest etiological groups of fibrillation has been studied in a group of thirty-six cases admitted to the London Hospital. The expectation of life is greater in that type which has often been referred to as the arteriosclerotic.

The influence of various other factors also has been considered. In mitral stenosis, cerebral embolism is shown to occur as frequently when the rhythm is normal as when fibrillation is present. When partial block is present apart from treatment, the outlook for patients with fibrillation is better. Fibrillation of the auricle does not appear to add to the gravity of a case in which complete block already exists; when the two disorders are combined, Adams-Stokes attacks have very rarely occurred. The prognosis is adversely affected by bundle-branch block. Premature ventricular contractions occurring spontaneously do not affect it.

The auricular oscillations of the electrocardiogram are generally smaller in the nonrheumatic than in the rheumatic type. There is little evidence of any relation between the duration of fibrillation and the amplitude of these waves.

Angina of effort, coexisting with fibrillation, was discovered five times in 2,000 patients with fibrillation. In coronary thrombosis the advent of fibrillation may or may not relieve the pain; relief seems more likely if congestive failure results.

Infective endocarditis and auricular fibrillation are both by themselves common sequelae of rheumatic carditis, but are very rarely combined. Death is not infrequently sudden in auricular fibrillation.

Schwentker, Francis F., and Noel, William M.: The Circulatory Failure of Diphtheria. III. The Treatment of the Circulatory Failure of Diphtheria. *Bull. Johns Hopkins Hosp.* 46: 359, 1930.

It is believed that in diphtheria intoxication there is a profound disturbance of carbohydrate metabolism. The disturbances following this intoxication usually become evident first in deficiencies in the circulatory mechanism, since this set of tissues can never be placed entirely at rest.

The authors suggest that carbohydrate in the form of dextrose be supplied to combat this disturbance. They have treated 14 patients with intravenous injections of dextrose. All of these patients were of the group showing signs of circulatory failure in the early stages of the disease and were so toxic that death was imminent. In 13 of these cases the patients recovered. In most instances the symptoms were rapidly alleviated; the temperature and pulse rate returned to normal, the toxic condition disappeared and convalescence was uneventful.

The authors recommend that 50 per cent solution of glucose be injected intravenously and that for each $\frac{1}{2}$ grams of glucose one unit of insulin be given intramuscularly. They believe that the power to utilize carbohydrates has been seriously disturbed in these patients and that the insulin is necessary to aid in using the glucose. Additional fluid should be supplied by the subcutaneous or intraperitoneal route, in order not to risk an added load on the failing circulation. These injections could be repeated depending upon the appearance of the patient.

Nye, Robert N., and Parker, Frederic, Jr.: Tissue Reactions in Rabbits Following Intravenous Injection of Bacteria. *Am. J. Path.* 6: 381, 1930.

The present paper deals with the methods used to produce the lesions in the body following the injection of bacteria, also a detailed description of the histological changes, is included.

The authors have found that following the intravenous injection of relatively large doses of various dead bacteria into rabbits there is a marked reaction of the tissue which contains cells of the reticulo-endothelial system. This reaction consists in an increase of lymphoid cells which are eventually transformed into, or replaced by, monocytes and giant cells. Such lesions ordinarily are temporary and result in no permanent damage. Identical lesions occur after the intravenous injection into rabbits of various colloidal substances.

They believe that such changes represent the reaction of normal rabbits to the disposition of foreign materials in the blood stream and have nothing to do with reactions secondary to sensitization or immunization.

Clawson, B. J.: Experimental Streptococcic Inflammation in Normal, Immune and Hypersensitive Animals. *Arch. Path.* 9: 1141, 1930.

Experimental streptococcic inflammatory lesions were studied by both gross and microscopic examination in animals under three specific conditions; normal, immune, and hypersensitive. The lesions studied were produced by the injection of small doses of streptococci into the subcutaneous tissues of rabbits.

The first group of normal animals had not had any previous injection and showed no agglutinins for streptococci at the time of the multiple subcutaneous injections. The second group of animals which had been given an immunized dose of streptococci intravenously showed agglutinins in the blood and some at the time of the secondary injections. The third group consisted of animals which had received one subcutaneous injection of agar of 45° C., heavily seeded with streptococci. Agglutinins in the blood of most of these animals were absent at the time of the secondary multiple subcutaneous injections and low at the time when the animals were killed. These animals were called the hypersensitive animals.

Experimental subcutaneous nodules with a polyblastic type of inflammation, similar to those seen in cases of human rheumatic infection can be produced in normal immune and hypersensitive animals by regulating the dose of the injection. These nodules can be produced with much smaller doses in the hypersensitive animals.

General immunity tends to retard the development of subcutaneous nodules except in cases in which the subcutaneous injections are made in from seven to twelve days after the primary immunizing inoculations.

The relationship between allergy and the pathogenesis of experimental rheumatoid subcutaneous nodules appears to be quantitative only.

Valentine, Eugenia, and Van Meter, Martha: The Localization of Streptococci in the Tissues of Rabbits. *J. Infect. Dis.* 47: 56, 1930.

In this investigation the lesions produced in rabbits following the injection of streptococci secured from the mouths of clinically healthy persons have been studied. Specimens from the tonsils and teeth of persons with evidence of focal or systemic infection were used for comparison. The ability of streptococci from these human sources to invade the tissues of rabbits following intravenous inoculation and to produce local pathological processes has been borne out and cultures especially of the alpha or green producing variety frequently localized in the joints and at times (13 per cent) in the heart, kidneys and other tissues regardless of the clinical

history of the person who furnished the specimens. There is some indication that these green producing streptococci have a greater invasive capacity for rabbits than other strains and produce heart lesions more frequently.

On the basis of this investigation, there is a tremendous variation in attempts to correlate the localization of streptococci in rabbits with the sources of the cultures. It does not appear that the ability of strains to localize is an inherent quality of the organisms associated with similar foci in the human host. It is not apparent what factors govern specific localization.

Derick, C. L., Hitchcock, C. H., and Swift, Homer F.: Reactions of Rabbits to Non-Hemolytic Streptococci. III. A Study of Modes of Sensitization. *J. Exper. Med.* 52: 1, 1930.

The most satisfactory method thus far found for the induction and maintenance of a high degree of hypersensitivity against nonhemolytic streptococci consists in the repeated production of small focal lesions with minimal doses of bacteria. The authors have studied the method of producing agar foci of infection in rabbits, in order to simulate conditions occurring in humans in relation to rheumatic fever. They believe that after a preliminary sensitizing period of about two weeks' duration with either large initial or small multiple daily inoculations, the later foci need be produced only at seven to ten day intervals.

Harrison, Tinsley R., and Pilcher, Cobb: Studies in Congestive Heart Failure. II. The Respiratory Exchange During and After Exercise. *J. Clin. Invest.* 8: 291, 1930.

Under basal conditions the individuals with congestive cardiac failure who were studied had increased ventilation, but their metabolic rates were usually normal. Exercise which produced no discomfort in normal subjects caused distress in the patients, and the degree of distress was usually proportional to the amount of edema. The ventilation increased more in the patients. The oxygen intake during the exercise was usually somewhat less and the oxygen debt correspondingly greater than in normal subjects. The total oxygen requirement was usually not changed. The excess carbon dioxide production during the exercise was often slightly greater, and immediately after the exercise it was usually considerably greater than in normal subjects. The patients with the most edema had the greatest carbon dioxide excretions.

The maximal exercise of which decompensated patients were capable was much less than for normal men. Maximal values for oxygen intake during exercise and for oxygen debt were much less in the patients than in the normal subjects. Maximum ventilation was also less. One cardiac patient who had never been decompensated on performing maximal exercise had an oxygen requirement and oxygen debt comparable to those of normal individuals but had a ratio of oxygen intake during exercise to oxygen debt comparable to that of the decompensated patients. One patient with mitral stenosis and only slight edema had a lower oxygen intake and carbon dioxide excretion during exercise than any other subject studied.

From these findings the following conclusions are drawn:

Subjects with mitral stenosis and only slight edema may suffer primarily from inability to increase their cardiac output per minute.

Subjects with edema and hypertensive heart disease may suffer from (a) a low maximum cardiac output; (b) impairment of oxygen utilization, so that with a given cardiac output per minute the oxygen intake is less; (c) diminished buffering power of the tissues.

In patients who have had edema of severe degree for a long time, the limiting factor, in so far as gas exchange is concerned, does not appear to be decreased oxygen intake but inability to acquire a large (normal) oxygen debt, and this discrepancy is believed to be due to impairment of tissue buffering power.

Pilcher, Cobb, Clark, Gurney, and Harrison, Tinsley R.: Studies in Congestive Heart Failure. III. The Buffering Power of the Blood and Tissues. J. Clin. Invest. 8: 291, 1930.

The P_H and carbon dioxide content of the blood of normal subjects and of patients with congestive heart failure has been studied before and after (a) administration of large doses of ammonium chloride, (b) breathing 5 per cent carbon dioxide and (c) a standardized exercise.

The findings in patients with heart failure at rest were usually within normal limits, but a state of acidosis was found in three patients with very severe symptoms. The changes occurring after administration of ammonium chloride and after breathing carbon dioxide were usually within normal limits in patients with congestive failure. The changes in P_H after exercise were usually greater in decompensated patients than in control subjects, and the degree of change was, with one exception, proportional to the extent and duration of the edema. This is believed to be compatible with the presence of diminished buffering power of the tissues in heart failure.

One compensated cardiac patient showed changes similar to those found in control subjects and one patient with noncardiac edema showed changes similar to those in the decompensated patients. This suggests that edema itself may be related to changes in the tissues of patients with heart failure.

Harrison, Tinsley R., Pilcher, Cobb, and Ewing, George: Studies in Congestive Heart Failure. IV. The Potassium Content of Skeletal and Cardiac Muscle. J. Clin. Invest. 8: 325, 1930.

The potassium content of the skeletal and cardiac muscle of individuals dying of congestive heart failure was found to be less than that of subjects dying without edema. The potassium content per unit of dry weight of edematous muscle was less than that of nonedematous muscle. This was true whether the edema was due to heart disease or not.

The suggestion is offered that loss of potassium with consequent diminution in the buffering power of the heart muscle constitutes a physicochemical factor in the production of "cardiac fatigue." In patients with congestive cardiac failure the decrease in potassium is believed to have been originally an effect of heart failure, but is considered as probably a secondary but important cause of subsequent breaks in compensation.

Pilcher, Cobb, Calhoun, J. Alfred, Cullen, Glenn E., and Harrison, Tinsley R.: Studies in Congestive Heart Failure. V. The Potassium Content of Skeletal Muscle Obtained by Biopsy. J. Clin. Invest. 9: 191, 1930.

The water content of pieces of gastrocnemius muscle removed by biopsy from patients with cardiac edema was invariably increased. The percentage of solids was correspondingly decreased. These changes usually persisted after clinical signs of edema had disappeared. The potassium content of the wet muscle from edematous patients was invariably abnormally low. The amount of potassium in the dry muscle was usually but not always diminished. As edema decreased, the potassium content of the wet muscle rose in three subjects; that of the dry muscle increased in two of them.

The administration of potassium dibasic phosphate was followed by a rise in the potassium content of the muscle.

Blumgart, Herrman L.; Gargill, Samuel L.; and Gilligan, Dorothy Rourke: Studies on the Velocity of Blood Flow. XIV. The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis. J. Clin. Invest. 9: 91, 1930.

Sixteen series of measurements were made in 7 patients with myxedema in order to correlate the clinical manifestations with changes in the velocity of blood flow, basal metabolic rate, pulse rate, plasma volume, venous and arterial pressures, respiratory minute volume and vital capacity of the lungs.

In each patient measurements when the basal metabolic rate was low were compared with subsequent measurements when the basal metabolic rate had been elevated to normal by appropriate doses of thyroid gland by mouth. The plasma volume per kilogram of body weight was low and tended to increase on administration of thyroid gland.

The pulse rate was low and bore a rough relationship to the basal metabolic rate. As the metabolism rose, the pulse rate approached normal. The venous pressure was within the normal limits of normal in all 7 patients.

The vital capacity of the lungs was strikingly diminished in all subjects in the absence of any signs of congestive heart failure and did not show significant change following treatment. The extent of diminution in the vital capacity was not closely related to the degree of lowering in the basal metabolic rate.

The respiratory minute volume was decreased before treatment and always rose significantly as the basal metabolic rate increased. The velocity of blood flow was strikingly slow in every subject and corresponded closely with the degree to which the metabolic rate was lowered. After taking thyroid gland by mouth, the rise in the metabolic rate and the increase in the velocity of blood flow to normal took place simultaneously and closely paralleled each other.

The slowing of blood flow in myxedema was almost as great as that observed in patients with rheumatic valvular heart disease with auricular fibrillation and symptoms and signs of congestive failure. None of the myxedematous patients showed clinical evidences of cardiovascular disease.

The great increase in velocity of blood flow and the consequent increased cardiac work that occurs when the basal metabolic rate is raised to normal affords a rational explanation of the clinical manifestations of cardiac insufficiency which occur not infrequently following thyroid gland therapy in myxedema.

The changes in the pulse rate, basal metabolic rate and velocity of blood flow in myxedema are compared to those previously reported in thyrotoxicosis. The comparison indicates that the increased velocity of blood flow in thyrotoxicosis results from the increased basal metabolic rate rather than from a specific toxic effect on the heart.

The findings emphasize the close interrelation between blood flow and metabolism and throw additional light on the degree, manner, and results of changes in the circulation associated with increased and decreased metabolic rates.

Blumgart, Herrman L., Gargill, Samuel L., and Gilligan, Dorothy Rourke: Studies on the Velocity of Blood Flow. XIII. The Circulatory Response to Thyrotoxicosis. J. Clin. Invest. 9: 69, 1930.

Twenty-seven series of measurements were made in thirteen patients with thyrotoxicosis in order to correlate the clinical manifestations with changes in the velocity of blood flow through the lungs, the basal metabolic rate, pulse rate, venous

and arterial pressures and vital capacity of the lungs. Measurements made when the basal metabolic rate was elevated were compared with subsequent measurements when the rate was reduced.

There was a general but inexact relation between the degree of elevation of the pulse rate and the increase in the basal metabolic rate. No significant deviations from the normal were observed in the venous blood pressure before or after treatment. Diminution in the vital capacity of the lungs was an inconstant finding. With a decrease in the basal metabolic rate, the vital capacity of the lungs tended to increase.

The velocity of the blood flow was strikingly increased so that the pulmonary circulation time was the fastest yet recorded in man. The increase in velocity of blood flow through the lungs was proportional to the degree of elevation in the basal metabolic rate. This emphasizes the strain under which the heart labors in thyrotoxicosis.

In nine patients with thyrotoxicosis but without circulatory failure, the basal metabolic rate averaged 33 per cent above the normal, while the velocity of blood flow through the lungs averaged 83 per cent above the normal. In 4 thyrotoxic patients with similar basal metabolic rates but with cardiovascular disease, the velocity of blood flow was slightly slower. The fact that the latter group of patients experienced dyspnea on slight exertion emphasizes the close interdependence of the circulatory-respiratory-metabolic mechanism. When the basal metabolic rate was lowered by the administration of compound solution of iodine or by operation, the velocity of blood flow was correspondingly slowed.

Morton, John J., and Scott, W. J. Merle: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities. *J. Clin. Invest.* 9: 235, 1930.

The importance of deciding whether a given peripheral vascular disease is due to vasospasm, occlusion of the lumen, or a combination of the two is recognized. Spinal anesthesia is offered as a test which will simplify the differentiation of these elements in the lower extremities. By its use the vasoconstrictor activity can be accurately measured by the rise in the surface temperature of the feet. The test is simple, safe, rapid, and localized to the part under study.

Under inhalation anesthesia surface temperatures show rapid changes in normal individuals and offer a possibility for a simple test for vascular lesions of the upper extremities.

Brown, George E.: Observations on the Surface Capillaries in Man Following Cervicothoracic Sympathetic Ganglionectomy. *J. Clin. Invest.* 9: 115, 1930.

Quantitative studies on the capillaries of the skin of human beings have been made both before and after cervicothoracic sympathetic ganglionectomy. Nine cases of advanced Raynaud's disease, four cases of vasomotor forms of scleroderma, four cases of primary scleroderma, two cases of thromboangiitis obliterans, and one case of arthritis of the hands have been studied.

The operation did not cause dilatation of the capillaries (the usual physiological effect) in any case. On the contrary, there were consistent narrowing of the dilated atonic capillaries in Raynaud's disease and an increase in the number of visible capillaries. This could be explained on the basis of a diminished concentration of a theoretical chemical dilator substance in the tissues.

Following sympathetic ganglionectomy in eight cases of vasomotor and primary forms of scleroderma, there was definite reduction in the caliber of the capillaries. The number of open capillaries for each square millimeter of skin increased.

There was quantitative evidence of arteriolar dilatation and lessened response on the part of these vessels to cold. Clinical improvement of some degree occurred in every case.

In the cases of thromboangiitis obliterans and arthritis, in which the capillaries were of fairly normal caliber and tonus, following operation no change in the width of the capillaries was noted. The intermittent slow flow of cyanotic capillary blood changed to one that was rapid, regular, and of normal color. The number of open capillaries was increased.

The major effect of sympathetic ganglionectomy is exerted on the arterioles. There is a sharp, maintained increase in the surface temperature of the skin of the hand in every case. These studies add some confirmation to the opinions of those who hold to the importance of chemical factors in modifying tonus in the capillaries of the skin of human beings. Chemical control of these vessels seems, under certain conditions, more effective than nervous control.

Brams, William A., and Strauss, Herman A.: The Effect of Amyl Nitrite on the Size of the Heart and the Width of the Aortic Shadow as Determined Roentgenologically. *Am. J. M. Sc.* 180: 618, 1930.

The size of the cardiac and the aortic shadow was studied roentgenologically in a series of 21 patients before and after administration of amyl nitrite. The group studied included 6 normal persons and 15 showing clinical evidence of arteriosclerosis with and without hypertension.

The transverse diameter of the heart shadow was reduced after amyl nitrite in 18 of the 21 persons studied. Presence or absence of arteriosclerosis or hypertension seemed to play a minor rôle in these changes in diameter. The width of the aortic shadow was increased in 13 of the 21 patients after amyl nitrite. This result also seemed to be independent of the condition of the peripheral vessels or degree of blood pressure. The changes in the cardiac diameter may perhaps be explained by the decreased content in the heart during diastole because of the rapid rate and displacement of blood into the dilated blood vessels and away from the heart.

Wiggers, Carl J., Theisen, Harold, and Williams, Harley A.: Further Observations on Experimental Aortic Insufficiency. II. Cinematographic Studies of Changes in Ventricular Size and in Left Ventricular Discharge. *J. Clin. Med.* 9: 215, 1930.

The changes in ventricular areas before and after production of an experimental aortic insufficiency were studied at constant heart rates, for the purpose of evaluating the percentile regurgitation. Successive photographs of the exposed heart, properly suspended in the pericardium, were taken at intervals of 0.031 second by means of a moving picture camera. Each photograph was subsequently projected, its outline drawn and the area measured. The values so obtained were plotted as curves and related to simultaneous records of aortic pressures and anteroposterior movements of the left ventricle. The advantages of the method and the precautions necessary in its employment are analyzed in detail.

The curves of outline changes during systole and diastole resemble volume curves in their general characteristics, but do not permit direct conclusions as to the degree to which the stroke of the left ventricle increased during aortic insufficiency. This is accomplished by applying Skavlem's formula, determining the increase in output and adding this to one-half the output of the two ventricles. By taking the left ventricular discharge so determined as a base, the percentile increase in stroke volume is easily calculated.

The results show that during aortic insufficiency the diastolic size is larger and the left ventricular discharge is increased from 16 to 58 per cent in different experiments, on an average 36.4 per cent. Factors other than heart rate and size of leak are responsible for the variations.

In the discussion it is pointed out that changes in heart size without data concerning the stroke volumes of the left ventricle are of no value in determining the percentile regurgitation, but that the percentile changes in stroke volume of the left ventricle give by inference a fair estimate of the percentile regurgitation.

The conclusion is reached that approximately one-third of the discharge during systole regurgitates through insufficient valves during diastole.

Dock, W., and Tainter, M. L.: The Circulatory Changes After Full Therapeutic Doses of Digitalis, With a Critical Discussion of Views on Cardiac Output. J. Clin. Investigation 8: 467, 1930.

Under experimental conditions in dogs a fall of venous pressure regularly accompanied the diminished cardiac output following a full therapeutic dose of digitalis. The authors believe that this is evidence that the change in blood flow was a result of peripheral and not of cardiac actions of the drug. Following a single therapeutic intravenous dose of digitalis, there was a gradual rise of blood pressure, sometimes sustained during several hours in animals which had not been operated on, and simultaneously there were constriction of the vessels of the skin and intestine and an increase in the volume of the liver and spleen due to hepatic vein constriction and to a pooling of blood in these viscera. These changes must have resulted in the diminished venous return to the heart and a diminished output and heart size.

The authors believe that these facts are in agreement with the generally accepted view that the output of the normal heart is governed largely by the venous return. The work of previous investigators has shown that the heart contracts with increased efficiency after therapeutic doses of digitalis but that the effect on cardiac output varies with the functional state of the circulation. The action of the drug in man probably varies in the same way; i.e., the output of the normal heart is reduced, but in such pathological states as heart failure with passive hyperemia, digitalis would tend to increase the cardiac output and to restore the venous pressure to a normal level.

Tainter, M. L., and Dock, W.: Further Observations on the Circulatory Actions of Digitalis and Strophanthus With Special Reference to the Liver, and Comparisons With Histamine and Epinephrine. J. Clin. Investigation 8: 485, 1930.

When dogs are given by intravenous injection doses of digitalis corresponding to the full therapeutic dose for man, they exhibit a rise in arterial and fall in right auricular pressure but a simultaneous rise in portal vein pressure. These changes are also caused by strophanthus. The fall in systemic and the rise in portal vein pressure are due to constriction of hepatic veins. After the liver was eliminated from the circulation by shunting the portal blood directly into the inferior vena cava or by ligating the arteries which supply the splanchnic area, digitalis or strophanthus did not cause a fall in venous pressure but in several instances raised it and did not cause as marked an elevation of arterial pressure as in the animals with the splanchnic circulation intact. Therefore, the fall in right auricular pressure, after giving digitalis to dogs with the hepatic circulation intact, was due to diminished venous return flow and ultimately to an accumulation of blood in the splanchnic or portal region as a result of obstructed hepatic outflow.

The experimental procedures used to determine the actions of digitalis and strophanthus were controlled by comparisons in the same organism with known

actions of histamine and epinephrine which cause a similar pooling of portal blood through a similar mechanism, the actions being modified, however, by changes in other vessels.

Weiss, Soma, and Ellis, Laurence B.: *Circulatory Measurements in Patients With Rheumatic Heart Disease Before and After the Administration of Digitalis.* J. Clin. Investigation 8: 435, 1930.

The purpose of the study presented here was to investigate a number of aspects of the circulation before and after the administration of digitalis in patients who were suffering from chronic rheumatic heart disease and who exhibited approximately the same clinical degree of circulatory failure. Repeated circulatory measurements were performed before and after digitalization in 4 patients with rheumatic heart disease. The patients were comfortable, at rest, exhibited no clinical evidence of congestive failure but showed marked reduction in their functional capacity on attempting any muscular activity.

The vital capacity of the lungs, the average cardiac output per minute and per beat, and the mean velocity of the blood flow were well below the normal. The velocity of the blood flow from the arm to face and the circulating blood volume were normal. While the average rate of blood flow was reduced as the result of heart disease, the exchange of carbon dioxide and oxygen between the capillaries and tissue per unit of the circulating blood volume was increased. The capillary circulation responded with increased efficiency in compensation for the impaired cardiac function.

Although all the patients showed clinical improvement as a result of the administration of digitalis, the cardiac output, the velocity of blood flow, the circulating blood volume, and the vital capacity of the lungs showed no significant changes. Certain aspects of the nature of circulatory failure in rheumatic heart disease are discussed. The evidence presented in this study and previous observations reported in the literature do not support the conception that the rate of blood flow is increased in circulatory failure because of rheumatic heart disease, nor that the beneficial effect of digitalis is manifested by its capacity to reduce the cardiac output.

Gold, Harry, and DeGraff, Arthur C.: *Studies on Digitalis in Ambulatory Cardiac Patients.* J. A. M. A. 95: 1237, 1930.

The following observations were made in the adult cardiac clinic of Bellevue Hospital on patients with auricular fibrillation with a view of determining the average daily dose of digitalis necessary to maintain the full therapeutic effects that had been induced when the patient was in the hospital. The authors have found that a much lower "effective concentration" of digitalis in the body suffices to produce full therapeutic effects than is required in the average bedridden patients in advanced congestive failure. They have found that in the ambulatory patient full therapeutic effects as judged by the usual clinical criteria of improvement can be produced by daily repetition of a relatively smaller dose of the drug that can then be continued as the daily maintenance dose without producing toxic symptoms.

It is pointed out that in the average ambulatory cardiac patient there is a wide margin between the minimum dosage that produces full therapeutic results and the maximum that can be tolerated without toxic symptoms. This margin is frequently smaller in patients with far advanced failure, and the latter often require the largest dosage that can be tolerated in order to produce the best results. The authors have developed the practice of using relatively large doses of

digitalis to produce the full therapeutic effects and then relatively smaller daily ones in order to maintain these results for long periods of time. They also believe that the explanation of this action is that the smaller doses are necessary in order to maintain the high "effective concentration" of the drug produced by the larger ones. Evidence has been set forth proving, however, that the "effective concentration" of the drug within the body necessary to maintain the effects is usually much lower than that required to produce them in the beginning.

Hyman, Albert S.: Resuscitation of the Stopped Heart by Intracardiac Therapy. Arch. Int. Med. 46: 553, 1930.

The success of an intracardiac injection procedure for the resuscitation of a stopped heart is apparently due more to the effect of the puncture wound made in the wall of the heart than to the chemical substance injected. The myocardium of the normal asystolic heart rapidly becomes irritable with the onset of anoxemia. Under these conditions any mechanical stimulation may irritate the heart to automatic contraction, and the success of massage and percussion of the heart for resuscitation can be explained on this basis. A puncture wound made by the injecting needle becomes a focus of increased irritability from which a stimulus for myocardial contraction may be developed. First contractions of the heart after injection are always extrasystoles, and the initial extrasystolic arrhythmia may give way quickly to a normal sinus rhythm with prompt recovery on the part of the patient.

However, when the period of anoxemia has been so prolonged or so intense that there is considerable disturbance in the electrodynamic factors controlling myocardial contraction, the initial extrasystolic arrhythmia may persist and may be quickly followed by a rapid sequence of ectopic beats. Such a condition leads to pathological fatigue of the ventricles which may be followed by ventricular fibrillation. Ventricular fibrillation is an extremely hazardous disturbance of the heart and is usually accompanied by immediate collapse of the circulation and death of the patient. This phenomenon explains the secondary collapse of the circulation often seen following what has apparently been a successful resuscitation of an asystolic heart. It is suggested, therefore, that the intracardiac puncture be made into the right auricle instead of into the ventricles as is now practiced. Intra-auricular puncture is not difficult and may be performed by using a slightly curved needle four or more inches long which may be inserted into the third interspace at the right sternal margin. The point should be directed toward the midline and to the patient's back. The distance to the right auricle measures about four inches or less, in children about two inches or less. The author points out that the danger of injuring the larger vessels is not great in this position, since they lie above and below this point.

The auricles are more responsive to mechanical stimulation than the ventricles. A mere prick of the needle may be sufficient to initiate contraction. The region of the right auricle reached by the needle is in general near the sinus node, and extrasystolic contractions arising from this location would spread over a more normal pathway than from any other location.

The sequential development of rapid auricular extrasystolic arrhythmia, auricular flutter, and finally fibrillation may not be of special significance so far as the ventricular output to the circulation is concerned, since the phenomenon of physiological block slows the ventricular rate.

Intra-auricular puncture should be attempted in every case of death that occurs as the result of the asystolic heart. The cases most favorable for resuscitation are those not affected by general or cardiovascular disease. In deaths occurring on

the operating table after hemorrhage, shock, anesthesia or other ill-defined conditions like status lymphaticus, prompt resuscitation may result from this procedure, either alone or combined with other life-saving measures, such as artificial respiration, transfusion, etc. In asphyxia neonatorum, it may be specific in its prompt initiation of automatic contraction of the heart.

The author describes nine cases which have been resuscitated by this method.

Blotner, Harry: Coronary Disease in Diabetes Mellitus. *New England J. Med.* 203: 709, 1930.

This paper presents a clinical study of 35 fatal cases of diabetes with coronary artery disease. Coronary sclerosis was found to occur in about 45 per cent of all diabetic cases brought to necropsy in the Peter Bent Brigham Hospital. The incidence of coronary disease is greater in diabetics than in nondiabetics, since it occurred in only 21 per cent of the nondiabetic group of patients above the age of forty years who were examined at autopsy.

Ten of the diabetic patients had no symptoms referable to the heart before they entered the hospital for the last time. Twenty-five had more or less significant cardiac symptoms from several months to ten years before they came under observation, but most of them entered the hospital for varying complaints which were not related to the heart. The chief cause of death in 43 per cent of all this series of diabetics was directly attributable to heart disease.

Cardiac infarction caused death in 10 per cent of 77 fatal diabetic cases and in 23 per cent of 35 fatal diabetic cases with pathological evidence of coronary sclerosis. Cardiac infarction is not an uncommon complication of diabetes and may be masked by the clinical picture of diabetic coma. Death from cardiac infarction occurred in three cases shortly after a rapid fall in blood sugar concentration following the administration of insulin.

The authors point out that due importance must be attached to the condition of the circulatory system in order to obtain the best therapeutic result in diabetes. A sudden lowering of the blood sugar concentration by insulin may be dangerous for the elderly diabetic patient with vascular disease; such a patient is likely to have sclerosis of the coronary vessels as part of generalized arteriosclerosis. The sudden lowering of blood sugar level by insulin may induce coronary thrombosis with a fatal outcome.

Kaiser, Albert D.: Results of Tonsillectomy. A Comparative Study of Twenty-Two Hundred Tonsillectomized Children With an Equal Number of Controls Three and Ten Years After Operation. *J. A. M. A.* 95: 837, 1930.

This is a further report on the study of a large group of children who were tonsillectomized previously and compared with a group of similar children without tonsillectomy. Outstanding benefits from the operation are apparent in influencing the incidence of sore throats over a ten-year period. Substantial benefits are apparent in rendering children less susceptible to scarlet fever and diphtheria. Cervical adenitis is decidedly reduced.

Acute head colds and otitis media are not essentially influenced over a ten-year period. Respiratory infections such as laryngitis, bronchitis and pneumonia not only are not benefited but occasionally occurred more frequently in this group of tonsillectomized children.

First attacks of rheumatic manifestations occur from 30 to 50 per cent less often in tonsillectomized children. The greatest reduction occurs in children tonsillectomized early. Recurrent attacks after tonsillectomy are not benefited at all.

Lennox, William G., and Leonhardt, Erna: The Oxygen and Carbon Dioxide Content of Blood From the Internal Jugular and Other Veins. *Arch. Int. Med.* 46: 630, 1930.

In a large series of patients the authors have measured the oxygen and carbon dioxide content of the blood from an artery and from various veins. The gaseous content of blood from the femoral vein was found to be the same as that of blood from the cubital vein. In sharp contrast blood from the internal jugular vein was more reduced and blood from the external jugular less reduced than blood from a cubital vein. These statements are true for average values. Measurements for individual patients vary widely.

In a series of 51 patients the average corrected respiratory quotient for blood from a cubital vein was 0.84 and from the internal jugular vein, 0.9. More sugar disappeared from the blood in its passage through the brain than in its passage through the arm. The former of these observations suggests that in the metabolism of the human brain, carbohydrates are unusually important.

Hurxthal, Lewis M.: The Appearance Time of T-Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion. *Arch. Int. Med.* 46: 657, 1930.

Two cases are reported in which records were obtained before and after coronary occlusion. Case 1 showed upright T-waves in all leads one hour after the onset of the attack, later followed by depression, whereas the record six days before the attack showed an inverted T-wave in Lead I. Case 2 showed a distinct but not diagnostic change one hour and fifteen minutes after onset.

The author points out that single tracings made following acute coronary occlusion may appear normal or if abnormal are of little value unless previous tracings have been taken or later records are obtained. At present one must rely on clinical diagnosis rather than on the electrocardiogram in an emergency in which surgical measures are concerned. It is suggested that electrocardiographic observations be made at more frequent intervals following acute coronary occlusion; such observations may prove of distinct value in diagnosis.

Palmer, Robert Sterling: The Treatment of Essential Hypertension. *New England J. Med.* 203: 208, 1930.

The author summarizes various treatments that have been proposed for this condition. The astonishing number of favorable reports on the use of a large variety of drugs and other forms of treatment in hypertension is an indication that more rigid criteria for the clinical evidence of a hypertensive effect must be met. The author suggests, therefore, that the following criteria might be useful in the clinical estimation of hypertensive action of any given therapeutic measure. It is only by satisfying some such minimum requirements as these that an adequate clinical evaluation may be made and the results of different investigations may be compared.

(1) Each observation shall consist of at least ten successive determinations of systolic and diastolic pressure at one-minute intervals, the same type of instrument to be used at each observation and the patient to be in the same position.

(2) On the whole, it appears advisable that this type of investigation be carried out, when possible, on ambulatory patients, exposed to the daily nervous excitements which the unhospitalized person must meet. The question of preliminary rest may be optional, provided it be always the same.

(3) Two or more, preferably more, weekly observations shall be made before starting treatment.

(4) A fall in the average of the ten readings at successive visits should be demonstrable after a period allowed for the full effect of the treatment, and this effect should be maintained at two or more further observations. The patient should be under treatment for four to six weeks.

(5) The treatment shall then be omitted and a rise in blood pressure shown after ample time has been allowed for the effect of the procedure to have abated.

(6) Finally, a second hypertensive effect of the treatment should again be demonstrable.

Stieglitz, Edward J.: Bismuth Subnitrate in the Treatment of Arterial Hypertension. J. A. M. A. 95: 842, 1930.

The author proposes the use of bismuth subnitrate in the treatment of arterial hypertension. He has observed the results obtained in two hundred unselected cases of hypertensive arterial disease and one hundred and twenty cases of hypertension in pregnancy and believes the results are satisfactory. The action of the drug is due to the fact that it is sparingly soluble in the intestinal tract, small amounts of nitrate ions being liberated continuously which on conversion into nitrous oxide by *Bacillus coli* leads to gradual vasorelaxation.

Weiss, Soma, and Ellis, Laurence B.: The Rational Treatment of Arterial Hypertension. J. A. M. A. 95: 846, 1930.

The authors believe that in a small proportion of cases the blood pressure will return to normal and the symptoms will disappear either permanently or for a prolonged period of time following the institution of approved methods. Such remission in the case of arterial hypertension may, however, occur spontaneously, and these individuals should live well-regulated lives and be followed carefully. In the second group, there will be some lowering of the blood pressure, although not to a normal level with accompanying subjective improvement, and some checking of the progress of the disease. A third and larger group of patients will show no material lowering of the blood pressure, but their symptoms will be lessened, and they will be enabled to live more comfortable lives. In certain of these by the careful regulation of their mode of living acute cardiovascular accidents will be averted, and to that extent their lives will be prolonged. The remainder, in particular many of the cases of malignant hypertension, will progress inexorably, apparently uninfluenced by therapy, to a fatal termination.

Book Reviews

LA TUBERCULOSE CARDIO-VASCULAIRE. LA COEUR DES TUBERCULEUX. By Adrien Pic, and Leon Morenas. Gaston Doin, Paris, 1930. Pp. 268 of text with 15 figures and 4 color plates.

The text is divided in three parts. Part one opens with an extensive discussion of tuberculosis of the pericardium, then takes up in order tuberculosis of the endocardium, valvular lesions of tuberculous origin, tuberculosis of the myocardium, idiopathic cardiac hypertrophy and its possible tuberculous origin and congenital lesions of tuberculous origin, altogether 131 pages. These various subjects are skillfully handled. The value of pericardiotomy for pericarditis is discussed as a satisfactory method of treatment. A satisfactory discussion of the diagnosis of tuberculous pericarditis is presented, including roentgenographic examination both without, and before and after, air injection in the pericardium. Tuberculosis of the cardiovascular system is not of common occurrence in the United States, though it is occasionally seen and is more often overlooked, either by failure to recognize the tuberculous nature of the pericarditis or by failure to recognize the pericarditis during the course of heart disease or tuberculosis. The condition must occur more frequently in European countries, however, since many case reports are included in this discussion and since it is known that other forms of more extensive and massive tuberculosis occur in continental Europe. This is particularly true of children and adolescents with large mediastinal abscesses, massive pulmonary and bone tuberculosis.

Part two discusses the heart of the tuberculous patient. Two important symptoms shown by these patients, palpitation and tachycardia, and their differential diagnosis are discussed. The physical and anatomical modifications of the heart receive deserved attention. Chapters on cardiac insufficiency in the tuberculous patient and combined heart disease and pulmonary tuberculosis are included.

Part three is concerned with tuberculosis of vessels, both arteries and veins, followed by a general résumé of the place of tuberculosis as compared with other infections of the cardiovascular apparatus. A very extensive and complete bibliography concludes the text. The book is well arranged, the discussions are clear, and complete and satisfactory diagnoses and illustrations aid the reader in following the subject. While the field of usefulness of the book will be limited somewhat by the extent of the subject, it makes a most satisfactory addition to those who are interested and have occasion to observe such patients.

H. McC.

HERZ, PULSATION UND BLUTBEWEGUNG. By Dr. Georg Hauffe. 246 pages, with 9 illustrations. J. F. Lehmanns, Munich, 1930.

Periodically a new volume is added to that small class of books which seek to upset orthodox conceptions in science and to replace them by revolutionary views of supposedly far-reaching significance. The book attempts to do this in behalf of the heart and circulation.

The editorial technique common to such endeavors is followed: Current views are not squarely treated, and the evidence accumulated in their support is lightly

brushed aside by facetious statements. This accomplished, a new hypothesis can easily be made to appear plausible through illogical misapplication of a few irrelevant observations on known physical principles.

Two radically new conceptions are developed:

(1) The rhythmic sequence of the heartbeat is conceived as due to mechanical properties of the elastic cardiovascular system rather than to a speculative up-building and discharge of an "inner stimulus." The tempo of the heartbeat is not given by impulses formed in and discharged by the sinus node, but is due to a movement externally transferred from the peripheral circulation to the cardiac muscle. The sinus node receives excitations; it does not initiate them. Initiation of stimuli occurs in the peripheral vessels as a result of vascular changes in sufficiently diffused regions.

(2) The heart and pericardium acting together form a combined force and suction pump operating somewhat after the following manner: Contraction of the ventricles expels blood into the aorta. This would dilate the aorta and raise the pressure during systole, as is commonly believed, but the author claims to have made the discovery that the size of the aorta becomes smaller and the arterial pressure falls during systole. This is explained as follows: Contraction of the ventricles in a pericardial sac of constant size serves to unfold the auricular wall, thereby enlarging its cavities. This creates a suction which draws blood into the auricles. But this is not all. The suction component is propagated peripherally through the veins and capillaries to the large arteries. When, on the other hand, the auricles contract, they fill the ventricle not only by the pressure created within but through the negative extracardiac pressure developed without. Lengthy explanations are given to prove that the feeble auricular contraction can indeed develop powerful effects and that the contractions of the auricular appendage determine the proper direction of the blood stream.

The critical reader who hopes to find the experimental proof for these revolutionary conceptions or even a logical set of arguments in their favor is doomed to disappointment. The theories are apparently based on certain physical experiments and clinical studies of the author. The former comprise the observations—which have apparently escaped all physicists—that increased velocity of flow decreases the diameter of elastic tubes. Furthermore, the author found that with a suitable velocity a rapid series of expansions and constrictions can be produced and made to travel over elastic tubes. By varying the velocity of flow, the frequency of such periodic disturbances can be changed, and even irregularities in rhythm can be inaugurated. These mechanical principles are supposed to be duplicated in the circulation.

The clinical observations seem to consist of the x-ray findings, that augmented minute output and increased blood flow cause a diminution in the aortic shadows and a fall in blood pressure. From this the author apparently leaps to the corollary that the size of the aortic and arterial pressure must decrease during systole. The reviewer has looked in vain for direct proof of this assumption.

The author is modest in his assertion that the work of Harvey is not completely upset by his hypothesis but is merely given a more far-reaching significance.

C. J. W.

THE MECHANISM OF THE HEART AND ITS ANOMALIES. By Emile Geraudel. Translated by Louis Faugères Bishop, Sr., and Louis Faugères Bishop, Jr. Williams and Wilkins Company, Baltimore, 1930.

This monograph is devoted to the presentation of the hypothesis that most of the disturbances of the heartbeat are the result of variations in blood flow within the specialized cardiac tissues. In the early chapters there is an account of the

technic of electrocardiography and a detailed description of the anatomy of the tissues mentioned with special reference to their blood supply.

The sino-auricular node is referred to as the "auriculonector," and the atrio-ventricular node, the His-bundle and its branches, as the "ventriculonector." The author believes that the former controls auricular, the latter, ventricular activity. He does not believe that the ventricles respond to the auricles, but thinks that the normal sequence of auricular and ventricular contraction is dependent upon a coördination of the activities of the two "cardionectors" brought about by the manner in which they are supplied with blood.

All of the common disturbances of the heartbeat are interpreted in terms of the hypothesis referred to. The evidence offered in support of this view is meager and unconvincing.

As an example of the views expressed regarding these disturbances, consider the following explanation of the abnormality of the ventricular complexes written by ventricular extrasystoles. Ventricular extrasystoles are premature beats but not ectopic beats; all ventricular beats originate within the "ventriculonector." In certain cases a premature beat is associated with a deformed complex because it occurs at a moment when the myocardium is not "normally relaxed." "The ventricle in particular, the cavity most often interested, is surprised *in flagrante delicto* by the activity of the cardionelector affecting it again and prematurely, and its new contraction will not be 'harmonious.'" Few will find this explanation preferable to the one now generally accepted.

The book may be recommended highly in some respects. It is excellently bound, and is printed in large clear type, on very good paper. The electrocardiograms are well reproduced; they are all legible, and all appear to be right side up. It seems fortunate that the book has been published in a limited edition. The appearance of the title page would seem to imply that the translating of a book is a much more important task than the writing of it.

F. N. W.

CLINICAL FEATURES OF HEART DISEASE. By Leroy Crummer, M.D., Emeritus Professor of Medicine, University of Nebraska. 415 pages, Paul B. Hoeber, Inc., New York, 1930.

In the second edition of this book the scope has been somewhat broadened by the addition of chapters on "rheumatic endocarditis" and "subacute bacterial endocarditis." The book remains essentially a clinical presentation, with emphasis on certain personal views of the author which in some instances have not yet gained universal acceptance. On the whole, however, it is an interesting and instructive volume which deserves the popularity it seems to have attained.

T. S. H.

The American Heart Journal

VOL. VI

FEBRUARY, 1931

No. 3

Original Communications

INSTRUMENTAL METHODS IN THE STUDY OF PERIPHERAL VASCULAR DISEASE*†

S. LEVY SIMPSON, M.A., M.D., M.R.C.P.
ROCHESTER, MINN.

INTRODUCTION

THE study of peripheral vascular disease lends itself to instrumental measurement and tends to become a more exact science. With the desire in modern medicine for mathematical precision, it is essential to recognize the limitations and fallacies of the methods applied, as well as their advantages. Unrecognized physiological variations may nullify what appear to be valuable pathological data.

The major part of this investigation deals with organic, occlusive arterial disease (chiefly thrombo-angiitis obliterans) and the effects of sympathetic ganglionectomy. The importance of clinical history and examination and the well-recognized postural tests cannot be over-emphasized. Nevertheless, much scope is still left for more exact methods of elucidating the state of disease and the results of certain procedures. The two most important instrumental methods of studying peripheral vascular disease are the measurement of surface temperature and oscillometry. Brown has stressed the value of the former method, and its comparative value is examined in this paper in relation to oscillometric measurement. The advantages and disadvantages of digital examination are considered, as are also the relative merits of the Tycos and Pachon oscillometers. Both instruments are made on similar aneroid principles, and record the amplitude of pulsations in arbitrary units. In the data given in this paper the Tycos measurements are expressed in millimeters and the Pachon, in half-units. The former instrument furnishes a permanent record, but in the use of the latter, the measurement must be noted at the time of examination and expressed numerically by the observer. In digital examination the

*Travelling Fellow, from the London Hospital, on duty in The Mayo Foundation, Rochester, Minn.

†Work done under the direction of George E. Brown, Division of Medicine, The Mayo Clinic, Rochester, Minn.

femoral, popliteal, posterior tibial, and dorsalis pedis arteries are palpated. It will be seen later that the different methods employed change their relative values when applied to different aspects of the problem and that they must therefore be considered under several headings. Although this work was commenced as a purely technical study with the advice and help of internists and neurologic surgeons of The Mayo Clinic, it has been found possible to observe and analyze several interesting and fundamental phenomena of physiological and pathological significance.

After some experience the digital palpation of superficial arteries offers no special difficulty. Occasionally pulsation in the warm fingers of an observer may simulate pulsation in the patient. The pulsation of a posterior tibial artery may not be obvious in a cold room and yet may be quite easily made out in a warm one. Palpation of an artery in a case of thrombo-angiitis obliterans by a previous observer may produce a temporary spasm which leads to an erroneous impression.

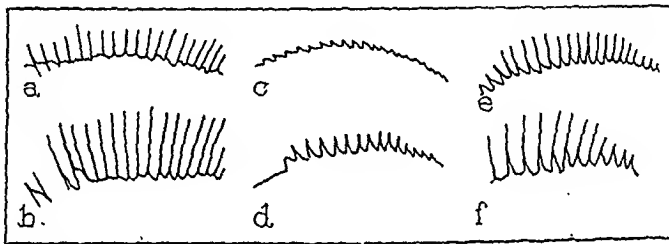


Fig. 1.—*a, b*, Variation in record of pulsations at the calf obtained by moving bag laterally; *c, d, e, f*, variation in pulsations at the ankle in different normal persons.

Even apart from these more obvious factors, it is not impossible for trained observers to differ, and to feel the need for the confirmation of digital impressions.

In using any form of oscillometer it is advisable to mark the exact site of measurement. The following sites may be taken: (1) femoral triangle; (2) immediately above patella; (3) immediately below patella; (4) 5 cm. below patella; (5) 10 cm. below patella; (6) 15 cm. below patella; (7) just above ankle, and (8) foot. In many cases measurements above the knee can be omitted. They tend to be less constant in view of the bulky musculature, and it is difficult to reapply the bag at the same site as before. Below the knee, a constant position in the horizontal axis or circumference of the limb is more easily attained. This can be done by placing the rubber valve connections along the anterior border of the tibia. There are two sites where false readings may be registered: (1) just below the patella, owing to the irregular contour produced by tendinous insertions, and (2) at the calf, owing to the large musculature. The latter is particularly well shown in Fig. 1 *a* and *b*. Both tracings were made 10 cm. below the patella, and the increased amplitude of the tracing shown in Fig. 1 *b*

was produced by shifting the pneumatic bag slightly to the outer side. This is the preferable point of application at this particular site. The readings at the lower border of the patella often appear to be reduced both in blood pressure and amplitude of pulsation and are thus somewhat anomalous. Five centimeters below the patella and just above the ankle joint are convenient sites in the leg to be used as a routine.

For the measurement of pulsation in the foot, palm, and fingers, it is advisable to use special pneumatic bags which can be connected to the Tyeos apparatus. The blood pressure recorded by the narrower pneumatic bag is, for mechanical reasons, considerably higher than that obtained with the larger bag usually employed, and therefore is not recorded in the tables. For similar reasons the amplitude of pulsation at the same site would be relatively higher with the smaller bag, but this is not obvious, owing to the smaller caliber of the vessels in the distal regions mentioned. These measurements made at the more peripheral points of the limbs will be seen later to be of very great significance.

TABLE I

OSCILLOMETRIC AND SPHYGMOMANOMETRIC VALUES FOR A NORMAL ADULT*

| SITE | DIGITAL PALPATION, GRADE | TYCOS APPARATUS | | | PACHON APPARATUS | | |
|-------------------------|--------------------------|-----------------|-----------|---------------------|------------------|-----------|---------------------|
| | | BLOOD PRESSURE | | OSCILLOMETRIC UNITS | BLOOD PRESSURE | | OSCILLOMETRIC UNITS |
| | | SYSTOLIC | DIASTOLIC | | SYSTOLIC | DIASTOLIC | |
| Femoral region | 4 | 170 | 100 | 26 | 200 | 120 | 20 |
| Above knee | | 140 | 90 | 22 | 170 | 100 | 16 |
| Popliteal region | 4 | | | | | | |
| Below patella | | 120 | 75 | 14 | 140 | 80 | 8 |
| 5 cm. below patella | | 125 | 80 | 20 | 150 | 80 | 15 |
| 10 cm. below patella | | 125 | 80 | 16 | 140 | 80 | 14 |
| 15 cm. below patella | | 125 | 80 | 12 | 150 | 80 | 10 |
| Ankle | | 125 | 80 | 8 | 150 | 80 | 8 |
| Posterior tibial region | 4 | | | | | | |
| Dorsalis pedis region | 4 | | | | | | |
| Foot | | | | 3 | | | |
| Brachial region | | 125 | 80 | 12 | 130 | 80 | 8 |

*Oscillometric values are given in the arbitrary units that are explained in the text. The grades used to designate the results of digital palpation are recorded in a scale of 4 to 0, in which 4 indicates maximal pulsation and 0, none. Blood pressure is given in millimeters of mercury.

6

In Table I are recorded a series of values for a normal adult. It will be seen that the oscillometric values correspond as far as relative values are concerned. The blood pressures registered by the Pachon apparatus tend to be higher than the real values. This is a purely mechanical factor and is of no particular significance when once recognized.

Although the values in Table I are supposed to be normal it would be more correct to admit that it is almost impossible to define normal

or average values. In Fig. 1, tracings *d*, *e* and *f* represent readings at the ankle in three separate adults about thirty years old, with no vascular abnormality. Tracings *e* and *f* were those of normal physicians and tracing *d* that of a patient with chronic gastric ulcer. The marked differences in the three are obvious. In the same figure, tracings *c* and *d* represent readings at the same site and of the same patient, but taken a few minutes apart. This rapid variation is unusual, and the small initial amplitude may possibly be due to emotional vasoconstrictor impulses. It is a potential fallacy that should not be ignored.

It is now possible to consider particular cases which reveal not only the correspondence or supplementary nature of the different methods of investigation, but also the relative advantages and disadvantages. The first study will be limited to an analysis of the exact severity of the disease, the degree and site of occlusion, and the degree of compensatory circulation.

DISCLOSURE OF SEVERITY AND SITE OF THE OCCLUSION

The following five cases are examples of thrombo-angiitis obliterans.

CASE 1.—A man, aged 47 years, had claudication at the arch of the left foot and ulceration of the fifth toe of the left foot. Digital examination (Table II) revealed good femoral pulsations on both sides, but complete absence of pulsation below the left knee. Oscillometry indicated very poor pulsations below the left knee and none in the left foot. The temperature of the left foot was also low. All methods indicated that the right leg was comparatively unaffected.

This case illustrates correspondence in results of different methods.

CASE 2.—A man, aged 38 years, had suffered from intermittent claudication of the calves of both legs for seven years. Two years before he came to the clinic the big toe of the right foot had been amputated elsewhere for gangrenous ulceration.

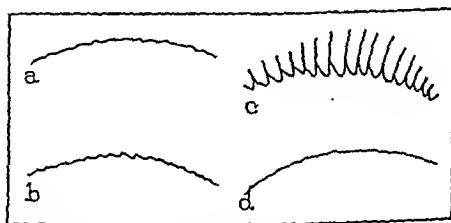


Fig. 2.—Quantitative diagnosis by oscillometric tracings in Case 2: *a*, right ankle; *b*, right foot; *c*, left ankle; *d*, left foot.

Healing had been obtained only after two further amputations, the latter of which was through the head of the metatarsal bone. Subsequently the right foot had given no trouble, but at the time of his visit to the clinic the second toe of the left foot was painfully ulcerated. Digital examination indicated complete absence of pulsation in the posterior tibial and dorsalis pedis arteries of both feet, from which it might be concluded that both extremities were potentially in danger of gangrene. This was not so. Oscillometric studies at the ankle gave evidence of very poor pulsations on the right side (Fig. 2 *a*) and good pulsations on the left (Fig. 2 *c*). In the foot, however, the position was quite reversed; pulsations were of moderate amplitude in the right foot (Fig. 2 *b*) and completely absent in the left (Fig. 2 *d*).

TABLE II
OSCILLOMETRIC AND SPHYGMOMANOMETRIC VALUES IN A CASE OF THROMBO-ANGITIS OBLITERANS

| SITE | DIGITAL PALPATION, GRADE | TYCOS APPARATUS | | | | | | FACHON APPARATUS | | | | | | |
|---|--------------------------|-----------------|-----------|---------------------|----------------|-----------|---------------------|------------------|-----------|---------------------|----------------|-----|---------------------|-----|
| | | RIGHT | | | LEFT | | | RIGHT | | | LEFT | | | |
| | | BLOOD PRESSURE | | OSCILLOMETRIC UNITS | BLOOD PRESSURE | | OSCILLOMETRIC UNITS | BLOOD PRESSURE | | OSCILLOMETRIC UNITS | BLOOD PRESSURE | | OSCILLOMETRIC UNITS | |
| | | SYSTOLIC | DIASTOLIC | | SYSTOLIC | DIASTOLIC | | SYSTOLIC | DIASTOLIC | | | | | |
| | | | | | | | | | | | | | | |
| Popliteal region | | | | | | | | | | | | | | |
| Lower border of patella | | | | | | | | | | | | | | |
| 5 cm. below patella | | | | | | | | | | | | | | |
| 10 cm. below patella | | | | | | | | | | | | | | |
| Ankle | | | | | | | | | | | | | | |
| Posterior tibial region | | | | | | | | | | | | | | |
| Dorsalis pedis region | | | | | | | | | | | | | | |
| Foot | | | | | | | | | | | | | | |
| Brachial region | | | | | | | | | | | | | | |
| Cutaneous temperature of toes, degrees C. | | | | | | | | | | | | | | |
| | RIGHT | LEFT | 130 | 85 | 7 | 120 | 85 | 5 | 120 | 80 | 3 | 100 | 60 | 0.5 |
| | | | 130 | 90 | 7 | 115 | 85 | 2 | 150 | 90 | 4 | 130 | 90 | 1 |
| | | | 130 | 90 | 4 | 105 | 80 | 1 | 150 | 110 | 3 | 120 | 100 | 1 |
| | | | 120 | 85 | 4 | 105 | 85 | 0.5 | 150 | 110 | 2 | 120 | 100 | 0.1 |
| | | | 130 | 80 | 1.5 | | | | 140 | 90 | | | | |

The right foot had been in greatest danger initially; the main arteries were occluded as far up as the calf. This foot, however, was now well nourished by the development of a collateral circulation as shown by the use of the small pneumatic bag, and was not likely to suffer from trophic trouble. The left foot, on the contrary, was threatened with gangrene and the vessels were occluded just above the internal malleolus.

It is obvious that in this case digital examination alone might give an incomplete and erroneous impression. This would also be true of oscillographic measurements limited to the ankle.

CASE 3.—A Roumanian Jew, aged 25 years, had a history of recurrent superficial phlebitis of the left leg over a period of seven months. Evidence of recent and organized superficial phlebitis could be seen on the ankle and leg. Oscillography revealed very good pulsation at the ankle and foot. Digital examination, however, revealed complete absence of pulsation at the site of palpation of the posterior tibial artery, behind the internal malleolus. The association with recurrent phlebitis rendered the diagnosis of localized thrombo-angiitis obliterans almost certain.

This case illustrates the importance of digital examination.

CASE 4.—A man, aged 34 years, had suffered from intermittent claudication of the left calf for one year, and from coldness and numbness of the left foot for eight months. The popliteal, posterior tibial, and dorsalis pedis arteries in the left leg were closed and pulsations were not recorded at the ankle. The right leg, however, was apparently unaffected, and all the vessels were open. Nevertheless, the surface temperatures of both feet were approximately the same, 29° C., and they gave no indication as to the true state of affairs. After lumbar sympathetic ganglionectomy, the temperature of the right foot was 35° C. and that of the left foot, 34° C.

This case illustrated the inadequacy of surface temperatures for diagnosis. In the majority of cases the surface temperature of an extremity, in which the main vessels are occluded, is lower than that of the sound limb. In these cases surface temperature is of diagnostic value. Apart from the numerous environmental factors which may obscure the significance of a single reading of surface temperature, a very important factor is the superimposed or primary effect of a vasoconstrictor element that may involve both limbs. This may render differentiation by readings of temperature impossible.

CASE 5.—A man, aged 43 years, had suffered from cold feet for several years. Five months before he came to the clinic the fourth toe of the left foot became infected and gangrene developed. Amputation at the base of the toe was successful; the wound healed. For one month the third toe had been persistently ulcerated. The fourth toe on the right foot was cyanotic. On digital examination all the vessels appeared to be open, and this was confirmed by oscillography; adequate pulsation was obtained even in the foot. Surface temperatures of the toes were all approximately 27° C. Postural tests disclosed slight pallor on elevation of the left foot, but no other changes.

Against the possibility of a purely vasospastic disorder were the following factors: the patient was a male; the gangrene of the left fourth toe was apparently

gangrene of the whole digit and only one toe was cyanotic; the postoperative temperatures were elevated but not maximal. The history and clinical considerations were the chief factors in arriving at a preoperative diagnosis. A modification of the oscillometric test gave a positive result. If the pneumatic bag was placed around the ankle and a pressure of 150 mm. was produced in it, and then the pressure was lowered by 10 mm. at a time, a dusky red color could be produced in some of the toes at a pressure of 110 mm. This localized dusky color does not occur in normal persons, and the test is apparently more sensitive than the dependency postural test, which was negative in this case.

This case illustrated the occasional fallacy of all methods. In cases of patients who present themselves with symptoms or signs of organic occlusion of the arteries of the extremities, it is usual to find the main vessels involved. On this fact depends the importance of digital examination and of oscillometric determinations. If, however, at the time of examination, the digital arteries alone are affected, such methods will give results which in themselves might lead to a fallacious conclusion.

The Pressure Gradient.—If determinations of blood pressure are made at the sites at which amplitudes of pulsation are recorded, it will be observed that with partial occlusion of large vessels there is a relation between the blood pressure and the amplitude of pulsation at any given point. In thrombo-angiitis obliterans, or arteriosclerosis with occlusion, the amplitude of pulsation tends to diminish from the knee downward toward the ankle. Coincident with this is a corresponding fall of blood pressure, and this might be termed "the pressure gradient." It is in striking contrast to the measurements in a normal person, in whom the pressure below the knee is approximately constant, down to and including measurements at the level of the ankle. Above the knee, even in a normal case, there is, however, some increase in pressure associated with increased size of arteries.

Fig. 3 shows the pressure gradient and amplitudes of pulsation in a case of arteriosclerosis compared with corresponding values for a normal person. The data given in the preceding cases of thrombo-angiitis obliterans disclose the same phenomena.

The Occult Blood Pressure.—If no record of pulsations or of blood pressure can be obtained at the right ankle, this does not necessarily mean that there is no blood flowing through the large vessels at this point. If the foot is blanched by elevation, and the pressure in a pneumatic bag around the ankle is raised above the anticipated normal pressure, then when the limb is lowered to the horizontal position and the pressure in the bag is gradually decreased by 10 mm. at intervals of two minutes, a point will be reached at which the foot is seen to become red. This indicates the pressure that is just inadequate to suppress the flow of blood to the foot at the point of measurement, the ankle, and might be termed the "occult blood pressure."

Comment.—The value of oscillometry in quantitative diagnosis of peripheral vascular disease is considerable. Quantitative diagnosis infers the complete elucidation of the exact degree and site of the disease. The Pachon apparatus and the Tycos apparatus are both suitable instruments, but the latter is of greater value in furnishing permanent and indisputable records and in lending itself more readily to examination of smaller and more distal regions. The latter examinations are often of great significance and may be the key to the condition.

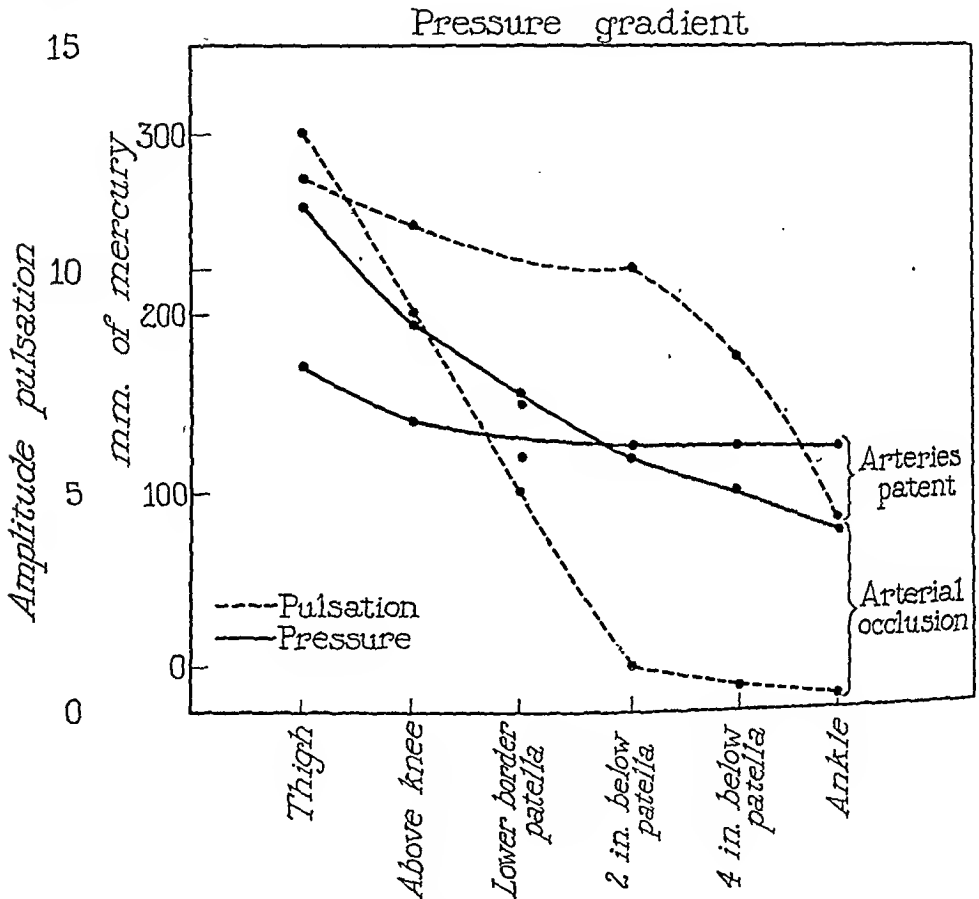


Fig. 3.—Pressure gradient and amplitude of pulsation in a case of arteriosclerosis compared with corresponding values for a normal person.

Digital examination is extremely useful and should not be dispensed with. In skilled hands it may give results as useful as those given by oscillometry, but for the average observer digital examination alone will not be used with the confidence or certainty with which oscillometry can be employed. Surface temperatures are not of great value for quantitative diagnostic purposes, although their importance in the complete study of vascular disease cannot be overemphasized. Clinical studies, postural and similar tests, all play an important part in diagnosis, and oscillometry is not intended to replace, but to supplement, other methods of investigation.

OSCILLOMETRIC STUDIES IN VACCINE FEVER

The response to fever produced by intravenous administration of typhoid vaccine has been used by Brown as an important factor in determining the suitability of cases of thrombo-angiitis obliterans for lumbar sympathetic ganglionectomy. His vasomotor index is determined after the temperature has been caused to rise by the vaccine and consists in the result of calculating as follows: the difference between the rise in temperature of the mouth and in the surface temperature

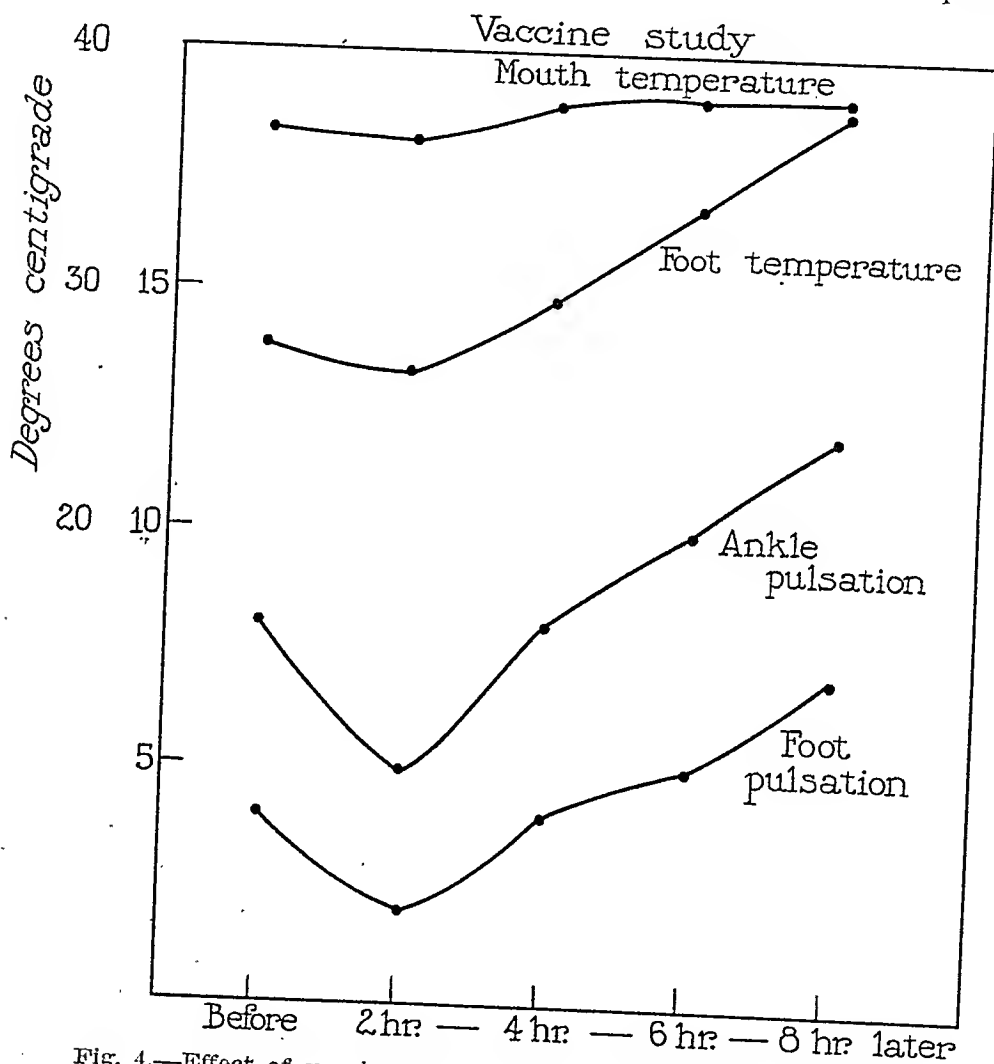


Fig. 4.—Effect of vaccine fever on temperature and pulsation.

of the foot, divided by the rise in temperature of the mouth.* An index of 2 or more has been taken to indicate a large element of spasm. Further vaccine fever produced at intervals of a few days often itself constitutes an important therapeutic measure. The present study was carried on to determine whether oscillographic readings (1) were definitely related to increased cutaneous temperature, (2) were of prognostic value, or (3) gave any indication of the potentiality of arteries to increase their amplitude of pulsation.

*The absolute increase in surface temperature with fever may be as satisfactory an index.

In order better to understand the mechanism of vaccine fever, preliminary studies were made in cases of polyarthritis in which the blood vessels were presumably free from organic disease, and therefore not limited in their power to respond.

Arthritis.—From Fig. 4 and Table III it will be seen that the amplitude of pulsation both at the ankle and at the foot appears to bear a direct relationship to the cutaneous temperature during vaccine fever. Although the increased amplitude of pulsation is associated with a rise in oral temperature, the correspondence is not maintained; cutaneous temperature and amplitude of pulsation continue to increase after the oral temperature has attained its maximal value. When there is a large vasospastic element, the oral temperature might rise as much as 2° C. without, at first, any gross change in the cutaneous temperature. Then, after five or six hours, with striking suddenness, both the cutaneous temperature and the amplitude of pulsation soar to a maximum, as if a controlling mechanism had been abruptly released.

TABLE III

OSCILLOMETRIC VALUES IN A CASE OF ARTHRITIS IN WHICH FEVER WAS INDUCED BY THE ADMINISTRATION OF VACCINE

| TIME | TEMPERATURE, DEGREES C. | | OSCILLOMETRIC UNITS, TYCOS | |
|----------------------|-------------------------|------|----------------------------|------|
| | ORAL | FOOT | ANKLE | FOOT |
| Before vaccine | 36.7 | 27.7 | 8 | 4 |
| After vaccine, hours | | | | |
| 2 | 36.3 | 26.8 | 5 | 2 |
| 4 | 37.8 | 29.6 | 8 | 4 |
| 6 | 38.0 | 33.7 | 10 | 5 |
| 8 | 38.0 | 37.7 | 12 | 7 |

It will be seen from Fig. 4 that in the first hour or two following the intravenous administration of vaccine there was a correlated fall in all measurements. This was associated with a sense of chilliness. If more frequent measurements are taken, it will be seen in some cases that there is a slight rise in cutaneous temperature and in oscillations before the fall. With larger doses of vaccine, especially in a hypersensitive person, definite rigor may occur and the prodromal phase may be much more marked. In some cases the foot becomes very cold and the pulsation at the ankle and foot may disappear. In cases of arteriosclerotic disease this, in rare instances, may be the cause of further thrombosis. It is thus advisable to avoid prolonged rigor. Barker has shown the value of typhoid "H" antigen for producing fever with little, if any, chill.

Some cases of arthritis have a large vasospastic element, and in these cases the pulsation of the foot or finger before vaccine is given may be minimal, and the resulting increased amplitude of pulsation very striking (Fig. 5).

Thrombo-angiitis Obliterans.—It has already been seen from the diagnostic studies that cutaneous temperatures are not necessarily an indication of the degree of patency or amplitude of pulsation of main arteries. This is due to the fact that the more immediate regulation of cutaneous temperature is the peripheral vasomotor mechanism which affects arterioles. Nevertheless, in many cases occlusion of main arteries is associated with diminution of cutaneous temperature. These considerations are further elucidated by a study of oscillographic tracings and cutaneous temperatures during vaccine fever in cases of thrombo-angiitis obliterans.

In Case 4 the left leg was chiefly involved; pulsation in the left ankle and foot were absent under ordinary circumstances, and those on the right side were good. Observations were made with both small and large doses of vaccine. With a dose of 25,000,000 bacilli the oral

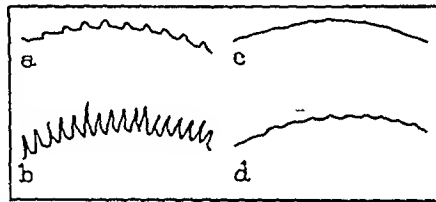


Fig. 5.—Effect of vaccine fever on oscillographic tracing in a case of arthritis: a, foot before fever; b, foot in course of fever; c, finger before fever; and d, finger in course of fever.

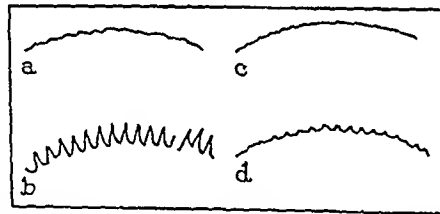


Fig. 6.—Effect of vaccine fever on oscillographic tracing in a case of thrombo-angiitis obliterans: a, right foot before fever; b, right foot in course of fever; c, left foot before fever, and d, left foot in course of fever.

temperature rose only to 37.2°C ., but the cutaneous temperature of the right foot rose 9.2°C ., from 25.6° to 34.8°C . Pulsations at the right ankle and right foot (Fig. 6) were actually doubled in amplitude. With a dose of 75,000,000 bacilli and a resulting oral temperature of 38.9°C ., the cutaneous temperature was 34.8°C . There is, therefore, no constant proportionate relationship between oral and cutaneous temperatures, although with the ultimate oral temperature of 40.1°C . the cutaneous temperature rose to 36.7°C . The amplitude of pulsation in the right ankle was no greater at this high temperature than at 37.2°C ., but that of the foot was still further increased. Pulsations in the foot are more closely related to cutaneous temperature of the foot than those in the ankle. In thrombo-angiitis obliterans pulsation may be constant, with marked variations in cutaneous temperature.

If one examines the sequence of events in the left leg of this patient, some interesting points are disclosed. In the first instance, with normal oral temperature, pulsation both at the ankle and foot (Fig. 6) was completely absent. Yet the initial cutaneous temperature was even a little higher than that on the right foot (left, 26.1°C .; right, 25.6°C .). With fever, the cutaneous temperature rose 9.9°C ., almost as wide a range as that of the right foot (11.1°C .); yet the pulsations that appeared at the ankle and foot were minimal (Fig. 6). Thus the effect of occlusion of main vessels does not necessarily prevent a considerable rise of cutaneous temperature; the latter is dependent on the ability of the arterioles to dilate fully, and presumably on the presence of adequate collateral circulation.

In contrast to the case just described, a case of thrombo-angiitis obliterans (Case 1) will be considered, in which the vasomotor index was poor and operation was contraindicated. The left leg was the one affected, and is the one which will therefore be considered here. With a dose of 125,000,000 bacilli, for the patient was refractory to smaller doses, the oral temperature rose 1.8°C . The cutaneous temperature, however, increased only from 28.7°C . to 32.6°C .; the vasomotor index was poor in this limb, namely, 1.2°C . The minimal pulsations at the ankle were hardly affected by the vaccine fever, whereas those at the foot were persistently absent. It is not uncommon for a poor index to be associated with persistent absence of pulsation in the foot, even at the height of fever. The latter, however, is not of absolute prognostic value, for a relative increase of cutaneous temperature may be obtained in the persistent absence of pulsation in the foot. It may be said, however, that under these circumstances the postoperative temperature of the skin rarely attains values greater than about 32.5°C . and is more often less than that. On the other hand, in the presence of good pulsation in the foot, at the height of fever, the postoperative surface temperature probably will be in the neighborhood of 34°C .

Comment.—The foregoing studies indicate the rôle of oscillography in determining the potentiality of arteries to dilate. When an artery is capable of dilatation, there is usually a relationship between temperature of the skin and amplitude of pulsation; this is much more true of the foot than of the ankle. The presence or increase of pulsation in the foot at the height of fever is of some prognostic value as to effects of ganglionectomy. Oscillographic measurements during fever give some indication as to the potentiality of arteries to increase their amplitude of pulsation. Studies of surface temperature are here of greater prognostic significance than oscillographic measurements.

VASCULAR STUDIES IN RELATION TO LUMBAR SYMPATHETIC GANGLIONECTOMY

Direct Study of Vasomotor Mechanism.—If an increase in amplitude of pulsation of peripheral arteries is to be considered as a possible therapeutic index, it is important to determine whether direct paraly-

sis or stimulation of a vasomotor nerve can affect such amplitude. Local anesthesia of the ulnar nerve at the elbow produced a rise of temperature in the little finger and a very marked increase in the amplitude of pulsation of the digital artery (Fig. 7 *a* and *b*). Similar results were obtained in the foot and even the ankle following spinal anesthesia. Mechanical stimulation of the fourth lumbar ganglion in man, during operation, produced marked diminution in the amplitude of pulsation at the foot and at the ankle (Fig. 8 *a* and *b*). It is concluded that vasomotor nerves can influence the amplitude of pulsation of peripheral arteries.

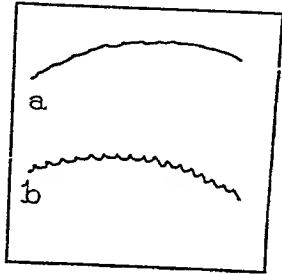


Fig. 7.

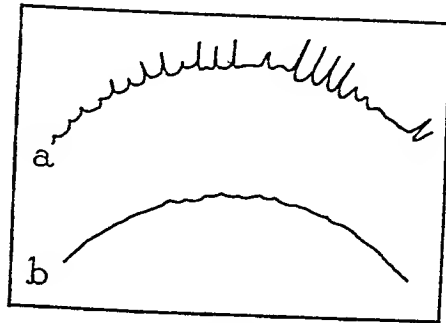


Fig. 8.

Fig. 7.—(*a*), Digital pulsation before anesthetization of ulnar nerve; (*b*), digital pulsation after anesthetization of ulnar nerve.

Fig. 8.—Mechanical stimulation of fourth lumbar ganglion: *a*, intermittent; *b*, constant.

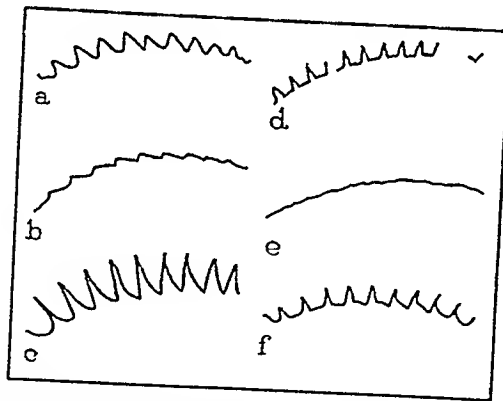


Fig. 9.—Stimulation of foot after lumbar sympathetic gangliectomy. A case of arthritis: *a*, exposure to atmosphere; *b*, immersion in cold water, and *c*, immersion in hot water. A case of thrombo-angiitis obliterans: *d*, exposure to atmosphere; *e*, immersion in cold water, and *f*, immersion in hot water.

Effect of Stimulation on Denervated Vessels.—The object of this investigation was to decide whether certain stimuli could affect the tone of an artery after severance of the vasomotor nerve. Cases of Raynaud's disease, arthritis, and Buerger's disease were studied at varying intervals after operation, from three weeks to five years. In all cases immersion of the foot in cold water (15°C.) for twenty to thirty minutes produced considerable diminution in amplitude of pulsation. This was most marked in the case of thrombo-angiitis obliterans, possibly because of the pathological state of the artery. Hot water (42°C.) for thirty minutes produced increased amplitude of pulsation (Fig. 9).

The complete severance of vasomotor nerves in these cases was shown by negative sweating tests. It is therefore concluded that heat and cold can probably act directly on the arterial wall.

Instrumental and Palpatory Methods.—Many workers in the field of peripheral vascular disease have cited increased amplitude of pulsation at the ankle as evidence in support of the value of a therapeutic procedure, medical or surgical. The failure to increase this amplitude similarly has been tacitly accepted as a negative or adverse result. It was therefore important to estimate accurately the value of oscillometry as a therapeutic index. The evidence obtained and considered

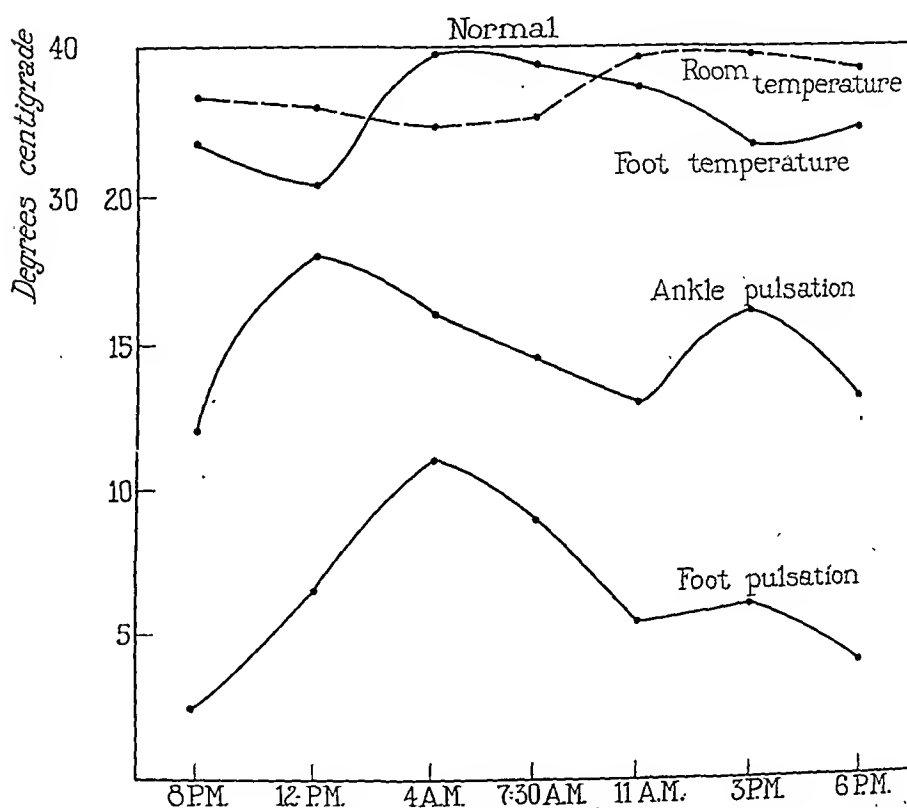


Fig. 10.—Physiological variations in pulsation in twenty-four hours in a normal person.

fully indicates that the assumptions just mentioned were often unjustified and took no account of numerous physiological variations. Oscillometric measurements in the foot, however, are of some relative value. Surface temperature will be seen to be of the greatest importance in estimating the effect of therapeutic procedures. Whereas it is usually recognized that surface temperatures must be taken under standard or controlled conditions, oscillometric measurements are nearly always recorded with complete disregard of such factors.

Physiological Variations.—Oscillometric measurements in ankle, foot and arm have been taken at intervals of approximately three hours throughout the day and night, and simultaneous readings of surface

temperature, room temperature, month temperature, pulse, and blood pressure have been made. Normal subjects, and patients with peripheral vascular disease have been studied, the latter before and after lumbar sympathetic ganglionectomy. The technical procedure was similar in all cases; surface temperatures were taken after the foot had been exposed to the atmosphere of the room for ten minutes.

The results in a normal adult are given in Table IV and Fig. 10, from which it will be seen that there is considerable variation in the amplitude of pulsation. The factors entering into this variation are complex and do not appear to lend themselves to exact analysis. It is obvious, however, that the unqualified statement of a preoperative oscillographic value is meaningless and does not offer any standard for subsequent comparison. The variation in the amplitude of pulsation is not constant for all persons, any more than do hourly readings of blood pressure give constant curves in all cases, or even for the same patient on successive days. Nevertheless in the cases investigated,

TABLE IV

PHYSIOLOGICAL VARIATION OF OSCILLOGRAPHIC AND SPHYGMOMANOMETRIC VALUES IN TWENTY-FOUR HOURS IN A NORMAL ADULT

| TIME | RIGHT ANKLE | | RIGHT FOOT | | | ARM | | | PULSE, BEATS EACH MINUTE | TEMPERATURE, DEGREES C. | |
|------------|-------------------|-----------|-------------------------------|-------------------------------|----------------------------|-------------------|-----------|-------------------------------|-----------------------------|----------------------------|------|
| | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | OSCILLOMETRIC UNITS, TYCOS | TEMPERATURE, DEGREES C. | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | | | |
| | SYSTOLIC | DIASTOLIC | | | | SYSTOLIC | DIASTOLIC | | | | |
| 8:00 P.M. | 145 | 85 | 12 | 3.5 | 31.8 | 135 | 80 | 13 | 80 | 36.8 | 23.3 |
| 12:00 M. | 165 | 90 | 18 | 6.5 | 30.4 | 150 | 90 | 20 | 75 | 36.7 | 23.0 |
| 4:00 A.M. | 160 | 85 | 16 | 11 | 34.8 | 145 | 90 | 22 | 80 | 36.8 | 22.3 |
| 7:30 A.M. | 170 | 100 | 14.5 | 9 | 34.4 | 155 | 95 | 30 | 66 | 36.7 | 22.6 |
| 10:30 A.M. | 160 | 90 | 13 | 5.5 | 33.6 | 130 | 90 | 15 | 72 | 36.8 | 24.6 |
| 3:00 P.M. | 140 | 90 | 16 | 6 | 31.7 | 125 | 70 | 26 | 81 | 36.9 | 24.7 |
| 6:00 P.M. | 160 | 95 | 13 | 4 | 32.2 | 140 | 80 | 16 | 84 | 37.0 | 24.2 |

the tendency to diurnal variations manifested itself. Pulsations in the foot appear to have some relationship to the surface temperatures, although this is not necessarily the case. Pulsations at the ankle are seen in Fig. 10 to be somewhat dissociated from the variation in surface temperature. This is only to be expected, for surface temperature is largely determined by a peripheral vasomotor mechanism which affects arterioles, whereas pulsations of the ankle are probably influenced in a greater degree by the state of the systemic circulation. Table V and Fig. 11 illustrate observations for twenty-four hours before lumbar sympathetic ganglionectomy in Case 4, an example of thrombo-angiitis obliterans.

Table VI and Fig. 12 show the results of observations in the same case three weeks after lumbar sympathetic ganglionectomy. The oscillographic curves are much flatter than they were before operation, indi-

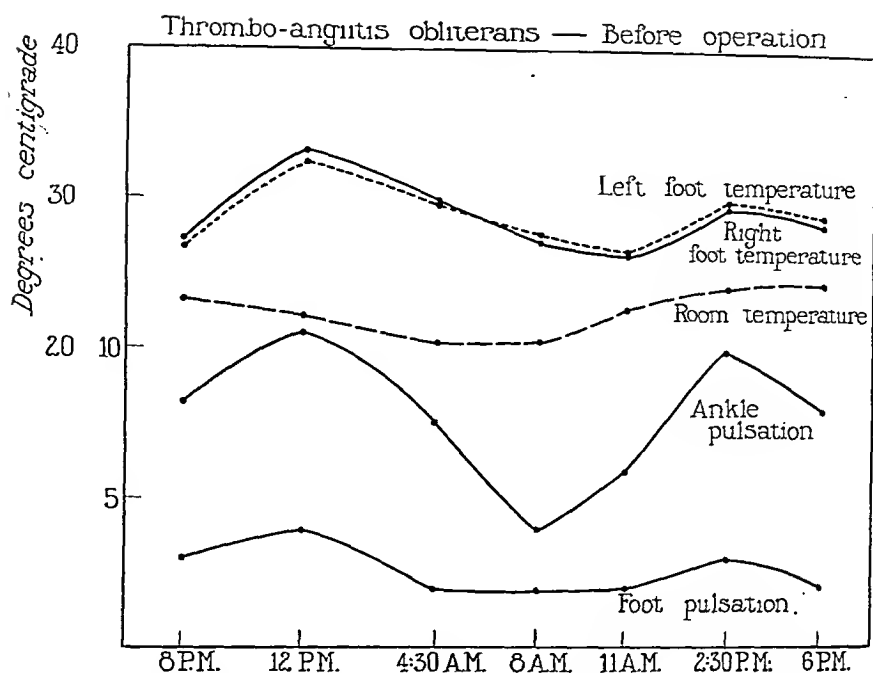


Fig. 11.—Observations for twenty-four hours before lumbar sympathetic ganglionectomy in a case of thrombo-angiitis obliterans.

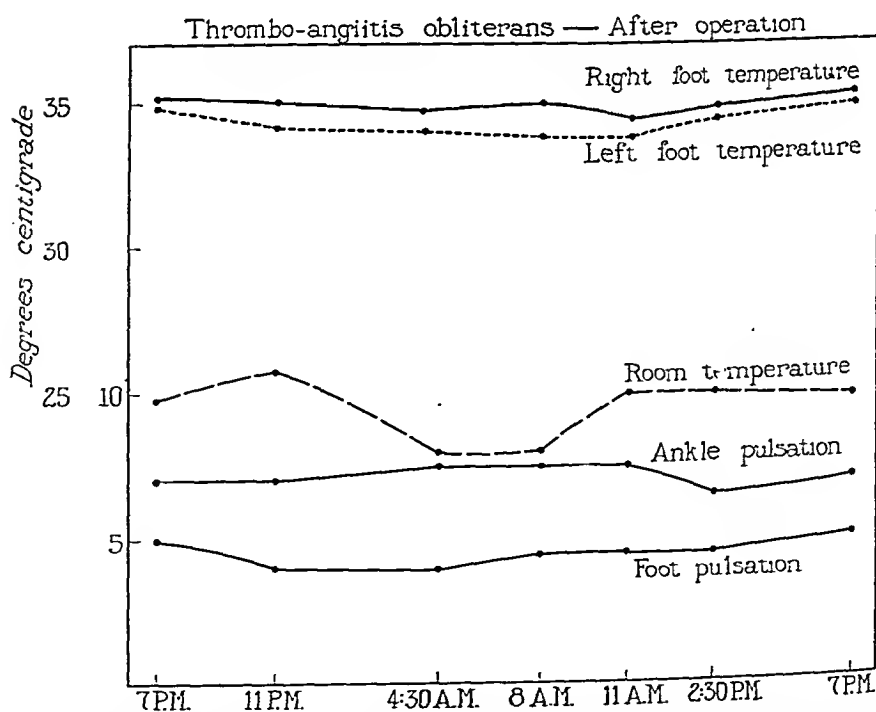


Fig. 12.—Observations over a period of twenty-four hours, three weeks after lumbar sympathetic ganglionectomy in the same case of thrombo-angiitis obliterans as that from which Fig. 11 was made.

eating less variation throughout the day. Observation in other cases, including cases of arthritis but not including any cases of organic arterial disease, indicates that this is usually so, although it is by no means always as marked as in this instance. Control postoperative observations made on patients with normal vascular systems, but with other lesions such as gastric ulcer, show that there are considerable variations throughout twenty-four hours. The most significant feature seen after sympathetic ganglionectomy is the persistent and almost invariable high surface temperature throughout the twenty-four hours. The values are markedly and constantly higher than before operation, and indicate the extreme importance of surface temperature as a therapeutic index. Further, this constantly high surface temperature has been found to persist in cases in which operation had been done five years before.

By comparing oscillographic readings in Case 4 at similar times of the day, it is seen that there is no postoperative increase in pulsation at the ankle; in fact, at many points there is an apparent decrease. In the right foot, however, there is a definite and fairly constant increase in amplitude of pulsation, and in the left foot pulsations have appeared which were absent before operation, except during the vaccine fever that was induced preoperatively. The latter point appears to be of prognostic value, intimating not only a relative increase of surface temperature, but an absolutely high temperature, usually greater than 32.5°C . It will be noted that postoperative temperatures are almost equal in the right and left leg in spite of the marked differences in pulsation between the limbs.

The vasomotor index in this case was good, greater than 2, and the temperatures attained in the two extremities during vaccine fever were, respectively, 34.8° and 34.9°C ., a close approximation to the postoperative surface temperatures. On another occasion, however, with a higher dose of vaccine, the oral temperature rose to 40.1°C . and the temperatures of the feet to 36.7° and 36°C ., respectively. This illustrates the fact that an oral temperature greater than 38.5° or 39°C . may not be optimal for prognostic purposes; the surface temperatures then may be in excess of their postoperative values.

The Immediate Postoperative Period.—During the first six hours or so after periarterial sympathectomy a negative phase* occurs (Leriche) in which both the temperature and the amplitude of oscillation are considerably less than that previous to operation. This has been attributed to irritative stimulation of the periarterial sympathetic plexus

*Following the negative phase, after operation there is a hyperactive phase, during which time all values are in excess of their ultimate attainment. It is perhaps analogous to the "reactionary phase" of Leriche but probably of different mechanism. The effect of general anesthesia cannot be ignored. Further, the hyperactive phase is almost always associated with some degree of postoperative fever. However, the higher oscillographic values may persist for a few days after the oral temperature has returned to normal. The vessels recover their normal pulsations toward the end of the first week.

TABLE V
OSCILLOMETRIC AND SPIRYGOMANOMETRIC VALUES FOR TWENTY-FOUR HOURS BEFORE LUMBAR SYMPATHETIC GANGLIONECTOMY IN A CASE OF
THROMBO-ANGITIS OBLITERANS, CASE 4

| TIME | RIGHT ANKLE | | | | RIGHT FOOT | | LEFT ANKLE OSCILLOMETRIC UNITS, TYCOS | LEFT FOOT | | BRACHIAL | | | | PULSE, BEATS EACH MINUTE | TEMPERATURE, DEGREES C. | |
|------------|-------------------|-----------|-------------------------------|-------------------------------|----------------------------|-------------------------------|---|----------------------------|-------------------|-----------|-------------------------------|------|------|-----------------------------|----------------------------|--|
| | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | OSCILLOMETRIC UNITS, TYCOS | TEMPERATURE, DEGREES C. | OSCILLOMETRIC UNITS, TYCOS | | TEMPERATURE, DEGREES C. | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | ORAL | ROOM | | | |
| | SYSTOLIC | DIASTOLIC | | | | | | | SYSTOLIC | DIASTOLIC | | | | | | |
| | | | | | | | | | | | | | | | | |
| 8:00 P.M. | 145 | 90 | 8.25 | 3 | 27.3 | 1.5 | 0 | 26.8 | 120 | 80 | 12 | 60 | 36.7 | 23.3 | | |
| 12:00 M. | 120 | 75 | 10.5 | 4 | 31.6 | 2 | 0 | 31.4 | 110 | 70 | 12 | 54 | 35.9 | 22.1 | | |
| 6:30 A.M. | 130 | 80 | 7.5 | 2 | 29.6 | 1 | 0 | 29.8 | 125 | 80 | 13 | 52 | 36.0 | 20.4 | | |
| 8:00 A.M. | 145 | 90 | 4 | 2 | 27.2 | 1 | 0 | 27.5 | 135 | 90 | 11 | 60 | 36.8 | 20.5 | | |
| 11:00 A.M. | 145 | 100 | 6 | 2 | 26.4 | 1.5 | 0 | 26.5 | 130 | 80 | 9 | 60 | 36.9 | 22.8 | | |
| 2:30 A.M. | 135 | 85 | 10 | 3 | 29.5 | 2 | 0 | 30.0 | 130 | 80 | 19 | 60 | 36.7 | 24.2 | | |
| 6:00 P.M. | 140 | 90 | 8 | 2 | 28.4 | 2 | 0 | 28.7 | 142 | 90 | 16 | 56 | 36.8 | 24.4 | | |

TABLE VI
OSCILLOMETRIC AND SPHYGMOMANOMETRIC VALUES FOR TWENTY-FOUR HOURS, THREE WEEKS AFTER LUMBAR SYMPATHETIC GANGLIONECTOMY IN
A CASE OF THROMBO-ANGITIS OBLITERANS, CASE 4

| TIME | RIGHT ANKLE | | | | RIGHT FOOT | | LEFT ANKLE OSCILLOMETRIC UNITS, TYCOS | LEFT FOOT | | ARM | | | PULSE, BEATS EACH MINUTE | TEMPERATURE, DEGREES C. | |
|------------|-------------------|-----------|-------------------------------|-------------------------------|----------------------------|-------------------------------|---|----------------------------|-------------------|-----------|-------------------------------|------|-----------------------------|----------------------------|--|
| | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | OSCILLOMETRIC UNITS, TYCOS | TEMPERATURE, DEGREES C. | OSCILLOMETRIC UNITS, TYCOS | | TEMPERATURE, DEGREES C. | PRESSURE BLOOD | | OSCILLOMETRIC UNITS, TYCOS | ORAL | | ROOM | |
| | SYSTOLIC | DIASTOLIC | | | | | | | SYSTOLIC | DIASTOLIC | | | | | |
| | | | | | | | | | | | | | | | |
| 7:00 P.M. | 125 | 90 | 7 | 6 | 35.2 | 2 | 0.5 | 34.8 | 125 | 80 | 16 | 70 | 37.0 | 24.8 | |
| 11:00 P.M. | 120 | 80 | 7 | 4 | 35.0 | 1.5 | 0.5 | 34.1 | 115 | 75 | 14 | 64 | 37.0 | 25.8 | |
| 4:30 A.M. | 120 | 80 | 7.5 | 4 | 34.8 | 2 | 0.5 | 34.0 | 130 | 80 | 11 | 70 | 36.5 | 23.0 | |
| 8:00 A.M. | 150 | 100 | 7.5 | 4.5 | 35.0 | 1 | 0.5 | 33.8 | 140 | 90 | 12 | 72 | 36.9 | 23.1 | |
| 11:00 A.M. | 135 | 90 | 7.5 | 4.5 | 34.4 | 1.5 | 0.5 | 33.8 | 130 | 90 | 9 | 70 | 36.9 | 25.0 | |
| 2:30 P.M. | 135 | 90 | 6.5 | 4.5 | 34.8 | 2 | 0.5 | 34.4 | 135 | 90 | 12 | 70 | 37.0 | 25.0 | |

and is followed by a positive phase of recovery and transitory over-compensation. Observations were carried out to determine whether such phenomena occur with lumbar sympathetic ganglionectomy.

TABLE VII

OSCILLOMETRIC AND SPHYGMOMANOMETRIC VALUES IN A CASE OF THROMBO-ANGIITIS OBLITERANS IMMEDIATELY AFTER AND REMOTELY AFTER LUMBAR SYMPATHETIC GANGLIONECTOMY

| TIME | TEMPERA- TURE, DEGREES C. | | ANKLE | | | ARM | | ROOM TEMPERA- TURE, DEGREES C. |
|------------------------|---------------------------------|------|-------------------|---------------|---------------------------------------|-------------------|---------------|--|
| | | | BLOOD PRESSURE | | OSCIL- LOMETRIC UNITS, TYCOS | BLOOD PRESSURE | | |
| | | | SYS- TOLIC | DIA- TOLIC | | SYS- TOLIC | DIA- TOLIC | |
| Before operation | 36.9 | 27.5 | 105 | 70 | 3 | 155 | 95 | 25.2 |
| After operation, hours | | | | | | | | |
| 1 | 35.0 | 29.2 | | | 0.1 | 100 | 70 | 24.4 |
| 3 | 35.6 | 29.8 | | | 0.1 | 112 | 70 | 24.6 |
| 7 | 36.7 | 30.6 | | | 0.5 | 120 | 76 | 25.2 |
| 10 | 37.0 | 30.9 | | | 1 | 130 | 80 | 24.8 |
| 13 | 37.2 | 31.2 | 100 | 70 | 2.5 | 140 | 90 | 24.4 |
| Day after operation | 37.2 | 32.6 | 100 | 70 | 3 | 145 | 90 | 25.0 |
| Three weeks later | 36.9 | 31.9 | 105 | 70 | 3 | 145 | 85 | 25.0 |

Table VII gives the data for a case of thrombo-angiitis obliterans which occurred in a man, aged fifty-three years, whose right leg had been amputated some years previously. It is seen that there was an immediate fall in amplitude of pulsation at the left ankle following lumbar sympathetic ganglionectomy and disappearance of pulsation in the foot; recovery commenced seven hours later. The chief cause of this, however, appears to have been a state of mild shock, for there was a corresponding fall of blood pressure and a subnormal oral temperature. This view was further confirmed by the occurrence, on the seventh day, of temporary unexplained jaundice associated with some degree of collapse. The pulsation in the ankle again almost disappeared, but attained a supernormal value following intravenous administration of saline solution. The cutaneous temperature was always greater than before operation, but there was a relatively negative phase since this temperature gradually increased with the increase of pulsation and recovery from shock. Pulsation in the foot in this case was minimal and did not increase either after operation or administration of vaccine. The final postoperative temperature was 31.9° C., as compared with the postvaccinal temperature of 32° C.

Apart from the major influence of shock, there may be a direct factor of irritation of nerves, for studies in the operating room tended to show that severe mechanical manipulation of lumbar ganglia was not followed by immediate complete recovery of the amplitude of pulsation.

Later Postoperative Period.—Oscillometric studies and observations of temperature were carried out daily throughout the postoperative period in a case of thrombo-angiitis obliterans in which the patient, a man, was aged forty-two years. The disease affected chiefly the left leg.

Table VIII gives the essential data. It will be seen that there was an immediate negative phase as described in Case 9, but the phase of recovery was more rapid. After five hours pulsation appeared in the left foot. This was completely absent before operation except at the height of the vaccine fever. The pulsations attained their maximal degree on the first day and then gradually disappeared on the seventh

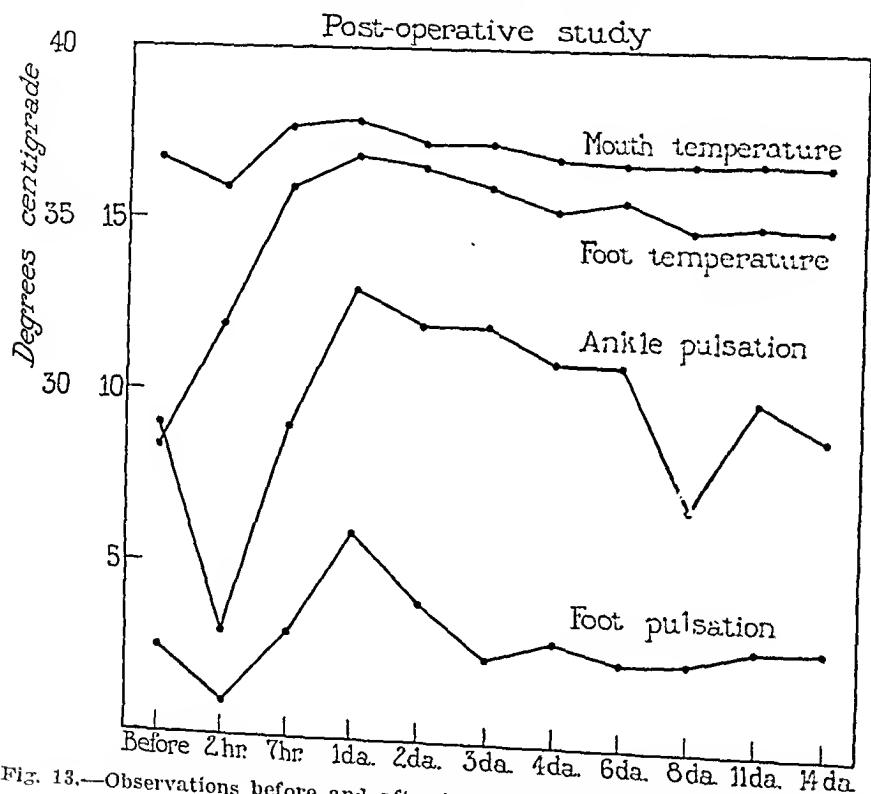


Fig. 13.—Observations before and after lumbar sympathetic ganglionectomy in a case of thrombo-angiitis obliterans.

day. Pulsations in the other foot followed a similar course, but were persistently present. Pulsations at the ankle were more variable, but oscillometric measurements on the whole gave little, if any, indication of the ultimate benefit of the operation (Fig. 13). The final temperatures of the skin, however, were 34.9° and 32.8° C. The good vasomotor index was completely justified.

It has been seen from these studies that the occurrence or increase of pulsations in the foot during vaccine therapy is of good prognostic significance, the ultimate postoperative temperature then probably exceeding 32.5° C. A further case of thrombo-angiitis obliterans will be cited to show that in spite of complete and persistent absence of pul-

TABLE VIII
OSCILLOMETRIC AND SPHYGMOMANOMETRIC OBSERVATIONS AFTER LUMBAR SYMPATHETIC GANGLIONECTOMY IN A CASE OF THROMBO-ANGITIS OBLITERANS

| TIME | RIGHT ANKLE | | | RIGHT FOOT OSCILLOMETRIC UNITS, TYCOS | RIGHT TOE TEMPERATURE, DEGREES C. | LEFT ANKLE | | | LEFT FOOT OSCILLOMETRIC UNITS, TYCOS | TEMPERATURE, DEGREES C. | | PULSE BEATS, EACH MINUTE | BRACHIAL BLOOD PRESSURE | | ROOM TEMPERATURE, DEGREES C. |
|-----------------------|-------------------|-----------|-------------------------------|--|--|-------------------|-----------|----------|---|----------------------------|----------|-----------------------------|-------------------------------|-----|------------------------------------|
| | BLOOD PRESSURE | | OSCILLOMETRIC UNITS, TYCOS | | | BLOOD PRESSURE | | LEFT TOE | | ORAL | SYSTOLIC | | DIASTOLIC | | |
| | SYSTOLIC | DIASTOLIC | | | | SYSTOLIC | DIASTOLIC | | | | | | | | |
| | | 130 | 90 | 9 | 2.5 | 28.4 | 110 | 60 | 2.5 | 0 | 27.8 | 36.7 | 76 | 120 | 80 |
| Before operation | | | | | | | | | | | | | | | |
| After operation, days | | | | | | | | | | | | | | | |
| 2 (hours) | 80 | 60 | 3 | 1 | 32.0 | 70 | 50 | 0.5 | 0 | 29.5 | 35.9 | 100 | 110 | 70 | 26.0 |
| 5 (hours) | 90 | 60 | 6 | 1 | 34.8 | 80 | 50 | 1 | 0.1 | 33.5 | 36.2 | 88 | 118 | 80 | 26.2 |
| 7 (hours) | 120 | 80 | 9 | 3 | 35.9 | 100 | 70 | 4 | 0.5 | 33.4 | 37.6 | 82 | 120 | 80 | 25.6 |
| 1 | 150 | 90 | 13 | 6 | 36.8 | 120 | 70 | 3 | 0.75 | 34.1 | 37.8 | 100 | 116 | 90 | 23.0 |
| 2 | 140 | 90 | 12 | 4 | 36.5 | 120 | 70 | 5 | 0.5 | 34.3 | 37.2 | 72 | 140 | 90 | 26.0 |
| 3 | 130 | 80 | 12 | 2.5 | 35.5 | 110 | 70 | 3.5 | 0.5 | 33.6 | 37.2 | 68 | 130 | 80 | 25.8 |
| 4 | 130 | 80 | 11 | 3 | 35.3 | 110 | 70 | 2.5 | 0.1 | 33.6 | 36.8 | 68 | 120 | 80 | 23.4 |
| 6 | 130 | 80 | 11 | 2.5 | 35.6 | 110 | 70 | 3 | 0.1 | 33.6 | 36.7 | 72 | 115 | 70 | 26.0 |
| 8 | 120 | 80 | 7 | 2.5 | 34.8 | 110 | 70 | 3 | 0 | 33.1 | 36.7 | 66 | 120 | 80 | 25.9 |
| 11 | 130 | 85 | 10 | 3 | 35.0 | 110 | 70 | 2.5 | 0 | 32.8 | 36.7 | 72 | 120 | 80 | 24.0 |
| 14 | 130 | 90 | 9 | 3 | 34.9 | 110 | 70 | 2.5 | 0 | 32.8 | 36.7 | 72 | 120 | 80 | 24.8 |

sations in the foot, a good clinical result can be obtained, associated with relative improvement in surface temperature. The preoperative temperature in the left foot was 24.2°C ., the temperature after vaccine had been given was 32°C ., the vascular index was greater than 2, and the ultimate postoperative temperature was 31°C .. The clinical result was good; an intractable and indolent ulcer healed completely, and the patient was relieved of pain. Although the final temperature was only 31°C ., the good vascular index was a reliable indication, since the relative increase in temperature was no less than 6.8°C . and the clinical result was excellent.

Postoperative Observations in a Case of Arthritis; a Control Study.—Since the previous study of thrombo-angiitis obliterans was subject to the comment that the arteries concerned were diseased, the following case of arthritis is of interest. The patient was a woman, aged twenty-six years, with arthritis in the hands and feet. The extremities were cold and clammy, and the vascular index was good. Oscillometric measurements were recorded at 2:30 P.M. and at an atmospheric temperature of 25°C . Tracings obtained at the foot, before operation, on the fourth day after operation (temperature 100.2°C .), and three weeks after operation, revealed that there was no ultimate increase in amplitude, although the preoperative surface temperature was 25.8°C ., and the postoperative, 36°C . This shows the marked superiority of surface temperatures as a therapeutic index and the enormous potential variation of cutaneous temperature, with constant amplitude of pulsation in the arteries. The amplitude of pulsations at the ankle in this case was actually less than before operation. The pulse, however, after operation tended to be slightly rapid; the rate was 92.

Comment.—Oscillometry as frequently practiced is entirely useless as a therapeutic index. Even with stated conditions of examinations, oscillometric values at the ankle tend to have a deceptive value owing to the difficulty of controlling all the physiological influencing factors. Similar comments are applicable, but apparently with less force, to pulsations in the foot. Not infrequently these are persistently greater than preoperative values, but this is by no means necessarily the case even with a considerable increase of surface temperature. Amplitude of pulsation is most likely to increase in such cases if there is a degree of spasm of the dorsalis pedis artery prior to operation.

The limited value of oscillometry as a therapeutic index is due to the fact that the chief action of the vasoconstrictor mechanism is on arterioles and not on arteries. The release of tonus of the arterioles is best detected by the measurement of surface temperature, which is a far better therapeutic index than oscillometry.

SUMMARY AND CONCLUSIONS

1. The relative value of mechanical methods of diagnosis in peripheral vascular disease is considered. The evidence shows that oscillometry is of value in determining the presence and amplitude or absence of pulsation.

2. The physiology and mechanism of vaccine fever is considered. Its prognostic value is found to be sound, and the vasomotor index seems to be the best single method of expressing it. Oscillometry in the foot during vaccine fever appears to have some prognostic value.

3. Stimulation and paralysis of vasomotor nerves affect arteries as well as arterioles.

4. Local hot and cold stimuli affect the amplitude of pulsation of peripheral arteries even after sympathetic ganglionectomy.

5. Results are reported of studies of physiological variation of amplitude of oscillations in normal conditions and in conditions of disease, throughout twenty-four hours. The variations are such as to render any single reading of little significance. The vasomotor mechanism can vary independently of amplitude of pulsation; the latter is considerably modified by general circulatory factors. Pulsations at the ankle are of little, if any significance as a therapeutic index. Pulsations in the foot are of some value as a therapeutic index.

6. Surface temperature is easily the best single therapeutic index. After sympathetic ganglionectomy surface temperature is found to be persistently high throughout day and night. This appears to be true for an indefinite period of years.

7. Oscillometry is of great value in the physiological study of pulsations in the larger peripheral arteries.

THE CLINICAL SIGNIFICANCE OF COMPLETE INVERSION OF LEAD III OF THE HUMAN ELECTROCARDIOGRAM

EDWARD F. BLAND, M.D.,* AND PAUL D. WHITE, M.D.
BOSTON, MASS.

ALTHOUGH inversion of all the deflections (P, QRS, and T) in Lead III of the human electrocardiogram (Fig. 1) is occasionally encountered, its clinical significance has not been sufficiently appreciated. Unlike most electrocardiographic findings, it is one that has largely escaped analysis and discussion. For comparison it is of interest to note that inversion of all complexes in Lead I has long been

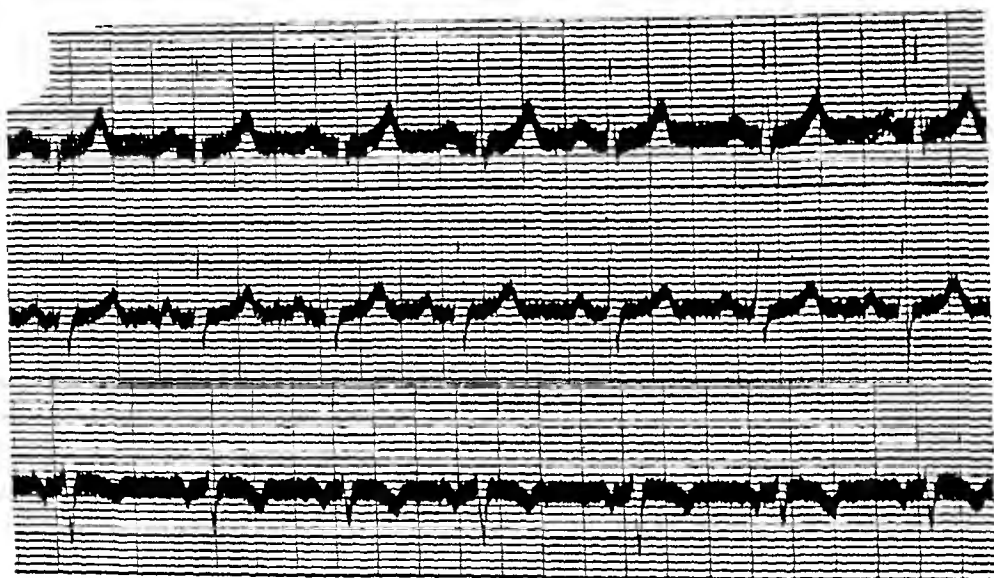


Fig. 1.—An electrocardiogram showing a complete inversion of the P, QRS, and T deflections in Lead III. Note the variation of the QRS amplitude in Lead III with respiration. Lead I corresponds to the usual normal Lead II.

recognized as evidence of congenital dextrocardia (Fig. 2), a condition almost the reverse of that giving rise to inversion of Lead III.

In the Cardiac Laboratory of the Massachusetts General Hospital we have encountered an inverted Lead III 115 times in a review of electrocardiograms of about 8000 patients, an incidence of 1 in 70. Without definite data as to the clinical significance of this finding, it has gradually come to be associated by us with a certain type of individual, most frequently an obese person, or one of a short and "stocky" build. The present investigation was undertaken in order to determine what significance, if any, one could attach to this electrocardiographic finding.

*Dalton Fellow, Cardiac Clinics and Laboratory, Massachusetts General Hospital.

Inversion of the P-wave alone or associated with other changes in the third lead has attracted the attention of numerous investigators. Einthoven, Fahr, and de Waart¹ pointed out that the P-deflection in Lead III may be considerably modified by the phases of respiration, being lower at the end of inspiration and the beginning of expiration, coinciding with the longer pauses of the cardiac cycle and perhaps depending upon an increase in the vagal tone at that time. However, they caution against attributing these changes entirely to the reflex influence of respiration, and add "that a slight rotation of the heart about the sagittal axis of the body, as is possible with a deep inspiration, is sufficient to modify conspicuously the form and height of the various complexes." Wilson² has reported several cases in which the negativity of the P-wave associated with respiration was ascribed to



Fig. 2.—An electrocardiogram of a patient with congenital dextrocardia showing an inversion of the P, QRS, and T deflections in Lead I for comparison with Fig. 1. Lead III corresponds to the usual normal Lead II.

a change in the location of the pacemaker; the possible occurrence of a change in the location of the pacemaker had been previously demonstrated by Lewis, Meakins, and White³ in experimental work on the dog's heart resulting from vagal stimulation. In 1919 Carter and Wedd⁴ presented additional evidence showing the effect of the vagi on a change in the location of the pacemaker and an inversion of the P-wave in Lead III. Furthermore, by taking leads from the chest wall Cohn⁵ demonstrated not only that the position of the heart in the chest has an influence on the form of the electrocardiogram but also that this influence may be far reaching. By rotating the leads in a clock-wise manner he produced an effect analogous to that which would be caused by rotating the heart to the left and upward, and the resulting electrocardiograms show left axis deviation with inversion

of the P- and T-waves as well as of the QRS waves in Lead III similar in all respects to those encountered in the series which we are now reporting.

In the present study we have collected clinical data on 100 patients whose electrocardiograms showed an inversion of all deflections in Lead III. The average age of the group was 47.3 years; 54 were females and 46 were males. The diagnoses were variable and covered a wide range of medical and surgical conditions. Organic heart disease was present in 55 of the patients, a percentage less than that of the incidence of heart disease in the cases routinely electrocardiographed at the Massachusetts General Hospital (which was 82 per cent of the last 100 cases, for example). Such heart disease was, moreover, only infrequently of considerable degree. Evidence of congestive failure, usually slight, was noted in 11 cases, and 15 patients had received digitalis therapy. Hypertension was present in 33 cases. From our data it seems that the presence or absence of organic heart disease is not an important factor in the inversion of Lead III. The amount of left axis deviation was usually of moderate degree; in only 17 of the patients did it exceed -30° by angle, and in only six -40° (Carter, Richter, and Greene⁶).

TABLE I

THE RELATIVE FREQUENCY IN 100 CASES OF FACTORS PREDISPOSING TO A TRANSVERSE POSITION OF THE HEART WITHIN THE CHEST

| | |
|---|----|
| Obesity | 55 |
| Ascites | 2 |
| Enlarged liver | 2 |
| Enlarged spleen | 1 |
| Large fibromyoma (uterus) | 1 |
| Right sided pleural effusion | 1 |
| Scoliosis of spine to right | 1 |
| Chest deformity (bulging of left side) | 1 |
| High diaphragm without obvious cause | 4 |
| Horizontal position of heart (roentgen ray) | 4 |
| Total | 72 |

In Table I is listed the frequency of certain factors, the presence of which predisposed to a rotation of the heart to the left and upward. It is seen from this table that marked obesity was by far the most common condition found (55 patients), and that in 72 patients (72 per cent) a transverse position of the heart was noted as the result of findings which were sufficiently pronounced to attract the attention of the physical examiner or of the roentgenologist in routine examinations, without attention having been previously called to this feature of the case. Of the remaining 28 patients in which there was no obvious cause for a transverse position of the heart, 24 were well developed and nourished, while 4 were thin and of the type in which one would expect a vertical position of the heart in the chest. Of this

latter group there was no evidence of organic heart disease in 3, while the remaining patient had chronic nephritis and hypertension with moderate cardiac enlargement, chiefly in the region of the left ventricle. In the group of 52 patients who had a roentgen examination of the chest, a high diaphragm was reported by the roentgenologist as a well-marked finding in 24 instances, and slight to moderate left ventricular hypertrophy was noted 41 times. Because of the frequent association of factors tending to elevate the diaphragm in this series, it is probable that the left ventricular "hypertrophy" noted by the roentgenologist was more apparent than real in a considerable number of the cases.

It is of further interest that in most of the subjects with total inversion of the electrocardiographic complexes in Lead III, forced respiration may be used as a diagnostic test. The deepest possible inspiration usually decreases markedly and sometimes abolishes completely the inversion of the complexes; deep expiration, on the other hand, increases the inversion in these cases but usually not a marked degree.

A study of the effects that the enlarged uterus in the later months of pregnancy may have upon Lead III would be of considerable interest, and we are planning to follow up this point. Although we have already found an inversion of the third lead in two patients who were pregnant, electrocardiograms taken after delivery showed essentially the same finding. Both of these women were, however, obese and of the type in which a high position of the diaphragm is frequently encountered.

From the present study we have found that our earlier impression was correct, namely, that the electrocardiographic finding of an inverted Lead III in the majority of instances is associated with a transverse position of the heart most frequently encountered in obese persons with a high diaphragm, and that it is otherwise of little clinical significance. Thus it is evident, as is also suggested by the work of Cohn,⁵ that the combination of left axis deviation with an inverted P-wave in Lead III indicates a rotation of the heart as a whole to the left, rather than left ventricular enlargement which might be suspected in a case with a like degree of left axis deviation but with an upright P-wave in the third lead.

From a somewhat different point of view Master and Oppenheimer⁷ arrived at conclusions in a large measure similar to ours. In a study of 100 obese persons they found in a considerable percentage (78 per cent of 73 cases studied by roentgen ray) an elevation of the diaphragm and a transverse position of the heart due to the presence of abdominal fat. "Electrocardiograms taken in ninety-seven cases showed definite characteristic changes. Fully 87 per cent showed a left ventricular preponderance, which not only is far beyond the number found in ordinary adults, but for the age groups studied, is an

unusually high figure. A change in the P- and T-waves in the third lead was very common; these waves were either flat (iso-electric) or inverted. The changes in the P-waves occurred in 70 per cent and in the T-waves in 87 per cent of the cases. . . . Repeated electrocardiograms were taken as the patients lost weight. Of fifteen patients whose average loss in weight was 32 pounds (15 kg.), all but two showed a return toward a normal electrocardiogram; that is, a change from inverted or flat to normal P- and T-waves, and a loss or diminution of the left ventricular preponderance."

SUMMARY AND CONCLUSIONS

The results of a clinical study of 100 patients with a complete inversion of Lead III of the electrocardiogram are presented. In 72 per cent of the series factors were found on physical or roentgenological examination which predisposed to a transverse position of the heart. Obesity was the most frequent condition encountered (55 per cent of the total series). A completely inverted Lead III in the majority of cases has little clinical significance, other than as an indication of the type of individual; namely, one in which are present conditions giving rise to a high position of the diaphragm and a transverse position of the heart.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms. *Pflüger's Arch. f. d. ges. Physiol.*, 150: 275, 1913.
2. Wilson, F. N.: Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated with Expiration. *Arch. Int. Med.*, 16: 86, 1915.
3. Lewis, T., Meakins, J. C., and White, P. D.: The Excitatory Process in the Dog's Heart. *Phil. Tr. Roy. Soc., London, Series B*, 205: 375, 1914.
4. Carter, E. P., and Wedd, A. M.: Observations on the Occurrence of Inverted and Biphasic P-Waves in Lead III of the Human Electrocardiogram. *Arch. Int. Med.*, 23: 1, 1919.
5. Cohn, A. E.: An Investigation of the Relation of the Position of the Heart to the Electrocardiogram. *Heart*, 9: 311, 1921-22.
6. Carter, E. P., Richter, C. T., and Greene, C. H.: A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram. *Johns Hopkins Hosp. Bull.*, 30: 162, 1919.
7. Master, A. M., and Oppenheimer, E. T.: A Study of Obesity. *J. A. M. A.*, 92: 1652, 1929.

ACUTE INTERSTITIAL MYOCARDITIS*

F. R. BAILEY, M.D., AND DOROTHY H. ANDERSEN, M.D.
NEW YORK, N. Y.

FIEDLER¹ in 1899 described four cases of "Acute Interstitial Myocarditis." In each of them the clinical picture was one of rapidly progressive myocardial failure ending in death. At autopsy the only characteristic finding was a diffuse cellular infiltration of the interstitial spaces of the heart muscle. In none of the cases was the etiology of the lesion determined.

Fiedler was not the first to describe this disease, as Steffen,² Freund,³ Rindfleisch,⁴ and Wolf⁵ had previously reported cases with similar clinical pictures and almost identical pathological findings. However, his name has become associated with this form of heart disease, and it is frequently described in the literature as "Fiedler's Myocarditis." Other terms used are acute, isolated, diffuse, and interstitial. Scott and Saphir⁶ have recently reported two cases which belong to this group. They have reviewed the literature on the subject and have found thirty-six cases in addition to their own. Three of these cases we felt should not have been included. One of them is the second case reported by Steffen.² In this instance the patient apparently recovered from an infection diagnosed during her life as acute myocarditis and later died of pulmonary tuberculosis. The pathological findings were not given. Another is Baumgartner's case,⁷ in which the findings were typical of tuberculosis of the myocardium. The third is the case of Rindfleisch,⁴ in which a *Staphylococcus pyogenus citreus* was cultured from the heart and in which the microscopic sections showed multiple pyogenic abscesses of the myocardium.

The variety of the clinical pictures presented by the cases which have been reported leads one to the conclusion that acute interstitial myocarditis is a pathological rather than a clinical entity. This is further borne out by the fact that in no instance has the correct diagnosis been made before death.

In the following case, while the autopsy findings were those of acute myocarditis, the clinical picture resembled closely that of coronary occlusion.

CASE REPORT

A hospital orderly, aged 39 years, came to the out-patient department of the Presbyterian Hospital on the evening of August 29, 1929, complaining of attacks of pain in the chest occurring at frequent intervals during the previous two weeks and usually brought on by exertion.

*From the Department of Medicine, Presbyterian Hospital, and the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Family History.—Noncontributory.

Personal History.—The patient was born in Ireland and came to this country when he was twenty-three years old. For the next five years he worked as a painter, but gave up this occupation because of "burning sensations in the stomach" and from that time on worked as a hospital orderly. He was not married. He did not use alcohol but smoked in moderation.

Past History.—In 1908, while still in Ireland, he had an operation for varicose veins. Shortly after coming to this country, while working as a painter at St. Luke's Hospital, he had a severe attack of diarrhea which required his spending about three days in the hospital. Fourteen others doing similar work had diarrhea at the same time. He was first admitted to the Presbyterian Hospital in May, 1920, suffering from acute gonorrhea. He made a rapid recovery and was discharged after a stay of only three days. Physical examination at that time revealed a heart slightly, if any, enlarged, the cardiac dullness extending eleven centimeters to the left of the midline in the fifth interspace. The sounds were described as being of good quality. The aortic second sound was louder than the pulmonic. No murmurs were heard. The blood pressure was 130/85 mm. The blood Wassermann reaction was negative in both alcoholic and cholesterol antigens. Early in the following year he received treatment for "arthritis of the feet" at the New York Orthopedic Hospital, and in July, 1926, he was treated in the emergency ward of the Presbyterian Hospital for a paronychia of the thumb.

There was no history of rheumatic fever or other previous acute infection. During the first few years of his stay in this country he had frequent colds, but no severe sore throats. Careful inquiry revealed no symptoms referable to the cardio-respiratory system prior to the present illness. He had not had nocturia. There was no story of syphilis or gonorrhea.

Present Illness.—For two weeks prior to his last admission the patient had been having fairly frequent attacks of mild pain starting in the region of the sternum, radiating laterally across the upper anterior part of the chest to the right and to the left, to the upper interscapular region on both sides, to both shoulders, and down the inner sides of both arms to the fourth and fifth fingers of both hands. These attacks of pain were associated with a feeling of tightness in the chest. They were quite definitely brought on by exertion and were relieved by rest. They were never very severe and were never associated with any fear. He had had no dyspnea, palpitation, nor edema of the ankles.

Physical Examination.—Revealed a rather obese man of 39 years, who did not look at all ill. His complexion was ruddy. His lips showed the very faintest cyanotic tinge. The pupils reacted well to light and during accommodation. The pharynx and tonsils were slightly injected. The lungs were clear, except for signs of moderate emphysema. The heart did not seem to be enlarged, though the obesity and barrel-shaped chest made percussion unsatisfactory. The sounds were distant, but of quite good quality. The aortic second sound was louder than the pulmonic. No murmurs were heard. The blood pressure was 160/100 mm. The radial vessels were moderately thickened. The pulses were equal and of good quality. The rate was not rapid. Examination of the abdomen revealed nothing abnormal.

It was felt at the time that the pain was cardiac in origin, due probably to disease of the coronary arteries. The patient was advised not to report for work that night, to attempt no exertion which seemed to him likely to bring on the pain, and to return to the employee's clinic the next day for a thorough examination.

He did not follow this advice, but worked most of the night. About six o'clock next morning, while in a street car on the way home, he was seized with a very severe pain in his chest, having the same distribution and radiation as those which he had had previously, but accompanied by a frightful sense of constriction under

the sternum and by a fear of impending death. He managed to get back to the hospital by taxi, vomiting once or twice on the way.

When seen in the emergency ward a few minutes later, he was groaning and writhing—apparently in very severe pain—sweating profusely. He said he felt as if his chest were being squeezed in a vise. His skin was cold and moist. His temperature was normal, his pulse not rapid. The heart sounds were much as they had been earlier in the evening, perhaps a little more distant. His blood pressure was 150/120 mm. Nitroglycerine, 0.0006 gm., was given without relief. This was repeated, with similar result. He was then given 0.016 gm. of morphine and moved into a bed in the overnight ward. He seemed to obtain relief from the morphine in a few minutes and fell asleep. An hour later he was still asleep, and his respirations were reported as being regular and of good quality. An hour after this the nurse in charge went to see him and found him dead. Inspection of the



Fig. 1.—Myocardium of the left ventricle. There are some necrotic fibers, but several normal fibers and a normal venule lie in the heavily infiltrated area.

body immediately after death revealed intense cyanosis of the face and mucous membranes. The skin of the body had a dusky hue.

The diagnosis made at the time of death was: General arteriosclerosis, arteriosclerosis of the coronary arteries, thrombosis of the coronary arteries, angina pectoris.

Pathological Findings.—The essential pathological findings were the following:

The body is that of an obese and muscular white man, 183 cm. in length. The face is red, the fingers and toes are intensely cyanotic. The pupils are equal and in extreme dilatation. The right leg has varicose veins and the scar of an old operation. There is no evidence of a recent wound or infection. The peritoneal cavity contains no free fluid. The peritoneal surfaces are normal. The liver extends 6 cm. below the xyphoid and 3.5 cm. below the costal margin in the right midclavicular line. The other relationships are normal. The right pleural cavity is obliterated by old fibrous adhesions, and a few old adhesions are present in the left pleural cavity. A large persistent thymus lies in its normal position. The pericardial sac contains a normal amount of clear fluid, and its surfaces are smooth and glistening.

Gross Examination.—The Heart weighs 460 gm. It is extremely flabby in consistency. Both ventricles are hypertrophied and dilated. The epicardium is normal, and there is a moderate amount of subepicardial fat. The right auricle and the tricuspid valve are normal. The right ventricle has thickened walls, measuring 0.7 cm. in thickness near the apex. The conus area is especially dilated, and the wall here measures 0.5 cm. The septum bulges slightly into the right ventricular cavity. The pulmonary valve is normal. The left auricle is normal. The mitral valve shows slight nodular thickening along the margin. Most of the chordae tendineae are normal, but there are several thickened ones which are attached to the posterior leaflet, far from the margin. The columnae carneae are prominent and the papillary muscles well developed. The dilatation of the left ventricle is shown chiefly by the bulging septum. The muscle is soft, very flabby, dark brown and uniform in color, without flecks. The aortic leaflets are soft, but there is some thickening at their attachment. There are several small atheromatous plaques scattered through the coronary arteries. There is no evidence of thrombosis.

Lungs: Right, 1080 gm., left, 640 gm. They are heavy, firm, dark purplish red without mottling or nodules. There is an abundance of blood-stained fluid on the



Fig. 2.—High power view of a small area in the infiltrated myocardium of the left ventricle, showing the types of cells present.

cut surface. *Spleen:* 380 grams. It is large and the capsule is tense. On section the bulging pulp is soft and friable, and much excess bloody fluid can be seraped from the surface. *Liver:* 3060 grams. It is firm, with rounded edges and a tense capsule. The cut surface bulges above the capsule, is soft and exudes blood-stained fluid. The branches of the hepatic vein are dilated. *Pancreas:* Normal. *Adrenals:* The left is atrophied, the right has a narrow cortex with a small lipid deposit. *Kidneys:* Right, weighs 260 grams, contains excess fluid, and is dark red in color. There are a few small hemorrhages in the pelvis. Otherwise normal. *Bladder:* Moderately hypertrophied and dilated. The mucosa is dull red and bears several minute cysts in the trigonum. *Prostate:* Moderately enlarged and contains three firm discrete nodules, each about 5 mm. in diameter, near the urethra. The medium lobe is prominent. *Testes:* Normal. *Stomach:* Normal, aside from several small submucosal hemorrhages. *Intestines:* Normal. *Thymus:* Weighs 40 grams. The lobular structure is preserved, but the outer portion of each lobule appears like a cortex of fat around the pinkish medulla.

Microscopic Examination.—*Heart:* A. Left Ventricle. In the myocardium and but a short distance beneath the endocardium lies a patch of edematous connective tissue infiltrated with many cells. The prominent cell is the polymorphonuclear leucocyte, although there are many eosinophiles and mononuclear phagocytes and oe-

casional lymphocytes and plasma cells scattered among them. In places there are also endothelioid nuclei. The muscle cells in the region are pressed apart. A few fibers are necrotic, but several normal ones traverse the center of the largest infiltrated area. Several small arterioles in the area have thickened walls without a corresponding increase in number of nuclei. This infiltrated area extends to the endocardium in one of the crevices between columnae carneae. The endocardium of the crevice is thickened and occupied by a dense mass of cells of the same types, except for the absence of eosinophiles, to the extent of ten or more cells deep. Throughout the remainder of the section there is a mild increase of cells in the interstitial tissue between muscle fibers, usually consisting of lymphocytes. There are scattered polymorphonuclears in one somewhat more densely infiltrated area. The muscle fibers vary in size, the fibrillae are conspicuous, and the lipochrome content small. The nuclei are normal. The epicardium and superficial fat are normal. No organisms are seen in the gram-stain.

B. Left Ventricle. At the deepest point of the inter-columnar crevices there are endocardial changes which are milder than those in heart A but similar to them.



Fig. 3.—Endocardium of the left ventricle. The base of an intercolumnar crypt found in the same section as Fig. 1 and in an adjacent field. The endocardium is densely infiltrated with lymphocytes, mononuclear phagocytes and polymorphonuclear leucocytes.

In one case the cellular infiltration extends up into the muscle for a distance of 0.6 mm. In the diffuse cellular infiltration and the normal muscle fibers this section resembles A.

C. Left Ventricle. There is one area of interstitial infiltration of the same types of cells found in A. There is some interstitial edema.

D. Septum. There is one small cluster of similar cells. The endocardium is slightly thickened but without any increase in the number of nuclei.

E. Right Auricle. Normal.

F. Sino-auricular Node. Normal.

G. Right Ventricle. Normal.

H. Left Auricle. Normal.

I. Mitral Valve. The marginal thickening of the valve consists of homogeneous material with occasional scattered round nuclei. The deeper portion of the section, corresponding to the middle of the valve, has many small blood vessels with scattered round cells about them. There are occasional endothelioid cells near them.

Other Organs.—The aorta shows early arteriosclerosis and engorgement of the adventitial vessels, with one small hemorrhage in the adventitia. The spleen is

congested, the Malpighian corpuscles are numerous and small with small hyalinized arterioles. The liver is congested and contains a moderate amount of fat. The adrenals are congested and have a moderate lipoid deposit. The pancreas is congested and contains several small hemorrhages. The kidneys show congestion. The mucosa of the bladder contains many minute cysts in the epithelium of the trigone. There are a few polymorphonuclear leucocytes in the prostatic tubules. Sections from the esophagus, stomach, intestines, and a bronchial lymph node show engorgement of the capillaries and venules. The medulla of the thymus contains a few lymphocytes and Hassall's corpuscles. The cortex is replaced by fat.

Anatomical Diagnosis.—Acute myocarditis. Acute endocarditis and valvulitis. Acute passive congestion of the lungs, liver, spleen, kidneys, adrenals, intestines, and lymph glands. Acute prostatitis, adenomata of the prostate. Moderate arteriosclerosis of the aorta. Persistent thymus gland. Fatty liver. Atrophy of the left adrenal. Cystitis cystica. Fibrous pleural adhesions.

DISCUSSION

In reviewing the clinical history in the light of the post-mortem results one finds little that could give one a clue as to the correct diagnosis. The cardiac pain which the patient had had for two weeks prior to his death was typical of that usually associated with disease of the coronary arteries. The sudden recurrence of this pain with great severity, its failure to respond to nitroglycerine, and the accompanying collapse with weakness, sweating, cyanosis, and sudden death, would lead one to expect that at autopsy one would find sclerosis of the coronary arteries with an occlusion of one of the larger vessels. The only discordant points are that the patient was below the age group in which coronary occlusion is common and that during the terminal attack of pain there was no fall in blood pressure.

Our failure to find anything in the history or physical findings that would have led one before the autopsy to make a correct diagnosis made it seem desirable to review the literature in an attempt to correlate the clinical pictures of the reported cases with the autopsy findings. This was not an easy task, as many of the histories are incompletely given, and in some cases the patients were moribund when first seen, and consequently no histories were obtained.

Table I shows the age incidence in the cases in which the ages were given:

TABLE I

| AGE | NUMBER OF CASES | AGE | NUMBER OF CASES |
|-------|-----------------|-------|-----------------|
| 1-10 | 3 | 41-50 | 5 |
| 11-20 | 2 | 51-60 | 2 |
| 21-30 | 13 | 61-70 | 1 |
| 31-40 | 4 | 71-80 | 1 |

It is interesting that while the disease may occur at any age, 40 per cent of the patients were in the third decade and 70 per cent were between twenty-one and fifty years of age. The sex was given in 32 cases. Of these 22 were males and 10 females, a ratio of over 2 : 1.

We were especially interested in the occurrence of pain and of sudden death. In no case was there a history of the type of pain usually described as anginal. Pain did occur in ten of the cases in which an attempt was made to give a clinical history. In seven of these it was described as precordial pain or oppression. One had epigastric pain and two had generalized cramp-like abdominal pains. In no case was pain the most striking symptom.

Sudden death without previous cardiac symptoms occurred in three cases. In none of these apparently was death preceded by a typical anginal attack. Gierke's⁸ patient, who had apparently previously been perfectly well, suddenly died "while beating the carpet." One of Saltykow's⁹ patients died suddenly while he was under treatment for a burn which was healing. One of Zuppinger's¹⁰ patients was being treated for an infection of the groin and suddenly was seized with "cramps" and died. Freund³ describes a patient who, after having polyarthritis for four months, suddenly went into coma and died. Two of the patients (Lemke's¹¹ and Schminke's¹²) were in acute heart failure at the time of the first examination, and no previous story was obtained. They died almost immediately. One patient described by Fiebach¹³ entered the hospital in acute heart failure and died the next day.

In the other 24 cases in which histories were given, the story was one of progressive myocardial failure. In those in which the down-hill progress was rapid, dyspnea and weakness were the outstanding symptoms, cyanosis and tachycardia the most frequently found signs. In those who ran a longer course, the story was usually one of dyspnea, weakness, and palpitation, with the gradual development of cyanosis, anasarca, and ascites, death usually being preceded by severe congestive failure. Table II shows the approximate durations of these cases.

TABLE II

| DURATION | NUMBER OF CASES | DURATION | NUMBER OF CASES |
|----------------|-----------------|-----------|-----------------|
| 1 week or less | 7 | 3 months | 3 |
| "A few days" | 2 | 4 months | 1 |
| 1 to 2 weeks | 4 | 8 months | 1 |
| 2 to 3 weeks | 1 | 9 months | 1 |
| 5 to 6 weeks | 1 | 1 year | 1 |
| 2 to 3 months | 1 | 21 months | 1 |

In none of the cases did examination of the heart during life give any clue as to the type of lesion present. In practically all, the heart was enlarged. The sounds were usually described as being of poor quality. None had murmurs suggesting endocardial lesions. In most of them the pulse was weak and rapid. Of the 23 cases in which the temperature was mentioned 17 had fever and 7 had normal or subnormal temperature.

The etiology of the disease has not been determined. Histories suggestive of rheumatic fever were obtained in only three cases. One of the patients reported by Scott and Saphir⁶ had had rheumatism twenty years before and a mild cardiac break ten years before. Stolz's¹⁴ patient had had polyarthrititis one year before. In only one case, Fiebach's,¹³ was there a history of previous syphilitic infection.

However, in reviewing the reported cases one is impressed by the number in which symptoms of decompensation started suddenly during or shortly after an acute infection. Kaufmann,¹⁵ in discussing this point, suggests that the myocardial lesions may be the result of the toxic action of bacterial products. In support of this hypothesis he mentions two cases of his own, of which one had an infected burn and the other an infection of the operative wound following the removal of tuberculous cervical lymph nodes. One of Saltykow's⁹ patients had a healing burn; the other had had an incision for drainage of an abscess of the jaw ten days before the onset of symptoms of heart failure. One of Sellentin's¹⁶ patients had had a carbuncle of the neck opened four weeks previously. Wolf's⁵ patient had a traumatic abrasion of the arm. Zuppinger¹⁰ reports a case in which an infection of the foot was incised thirteen days before the onset of cardiac symptoms. His other patient had a skin infection of the left groin. One of Fiedler's¹ patients had been troubled for some time with leg ulcers, and another had previously had a hemorrhagic skin eruption. In most of these cases death came suddenly or after a very short and rapidly progressive illness. "Grippe" preceded the onset of cardiac symptoms in Hafner's¹⁷ case and in one of the cases reported by Scott and Saphir.⁶ Fiebach¹³ reports a patient whose illness started with a cold and high fever. Bilateral otitis media (Pfeiffer bacillus) developed, soon to be followed by symptoms of decompensation. Death occurred eight days after the onset. Pal's¹⁸ patient had had acute gonorrheal urethritis two months before the onset.

While there is no proof that these infections were the causative factors in the production of the myocarditis, one cannot avoid being impressed by the large number of cases in which they preceded very closely the onset of myocardial failure.

A fairly full pathological study has been reported in thirty of the cases in the literature. These cases are those of Freund,³ Wolf,⁵ Fiedler¹ (four cases), Jossierand and Gallavardin¹⁰ (three cases), Zuppinger¹⁰ (two cases), Sellentin¹⁶ (two cases), Saltykow⁹ (two cases), Cohn,²⁰ Pal,¹⁸ Fiebach¹³ (two cases), Gierke,⁸ Shilling²¹ (two cases), Schminke,¹² Hafner,¹⁷ Stoltz,¹⁴ Lemke¹¹ (first case), Mordre,²² Scott and Saphir⁶ (two cases), and our own case.

The one constant pathological finding is the presence of changes in the myocardium, and these changes are consistently the same only in the microscopic sections. In every case there are also gross changes in

the heart. In the majority of cases the heart is hypertrophied to a moderate degree, although in the two cases reported by Scott and Saphir,⁶ and in Wolf's Case 5 the heart weighed over 600 grams. In three of the five cases without hypertrophy death occurred within a few days after onset, and in the other two the interval is not stated. On the other hand, in thirteen of the patients who died less than two weeks after the first onset of symptoms, and in several of the cases of sudden death, there was definite hypertrophy, indicating a process of much longer duration than the symptoms. The hypertrophy is always of the left ventricle and sometimes also of the right. There is dilatation of the ventricles in most of the cases. Usually the left ventricle is dilated, and in many cases both are affected equally.

The most prominent lesion is always in the myocardium. When the consistency of the muscle is mentioned, it is usually said to be extremely flabby (nine cases), as in the present case, although in other instances (five cases) it is firm. An attempt to correlate this point with the duration of the disease shows that the flabby myocardium is more often associated with a brief course and the firm one with a more prolonged illness, but that there are exceptions in both case groups. In twenty-three of the thirty cases the myocardium is described as mottled with greyish-yellow streaks and flecks which show through the endocardium but appear most clearly on the cut surface of the muscle. The left ventricle and sometimes the right are involved, although the auricles sometimes have the same appearance. The muscle between these pale spots is usually very dark red. This description is so consistently met with that it is surprising to find five cases, including the one here reported, in which there was no gross abnormality in the color of the heart muscle. In four cases it is a homogenous dark red, and in the fifth it is described as greyish-red. The presence of mural thrombi in ten cases is also not surprising. The thrombi are most often in the apex of the left ventricle; in two cases they are in the apex of the right ventricle; in one case, in both ventricles, and in two cases in the left auricle. In eight cases the expected widespread infarction of the viscera is found. The presence of thrombi can be correlated with the duration of the disease. Mural thrombi were present in eight of the ten cases with symptoms extending over one month or more. Mural thrombi were also present in Shilling's case²¹ of fourteen days' duration and in Fiebach's case¹³ of one day's duration. The case here presented shows acute endocarditis involving the crevices between the columnae carneae (Fig. 3), and it is easy to conceive of thrombus formation on such a surface.

In four of the cases there was nodular thickening of the mitral valve, and in one there was thrombosis of the anterior descending branch of the left coronary artery, with beginning infarction of the area supplied by it. There were no other complicating heart lesions.

The microscopie picture of the myocardium is singularly uniform. There is an infiltration of many cells with lymphocytes and mononuclear phagocytes as the most numerous cell types, and with eosinophiles, polymorphonuclear leucocytes and fibroblasts in lesser numbers. These cells are found in clumps or scattered among the muscle fibers singly, or they lie in the perivascular connective tissue. Many minor changes in the muscle fibers have been reported, but these appear to be secondary in importance. There are a few necrotic fibers in and around the foci of invading cells, and sometimes multinucleated fragments of muscle cells. In several cases of longer standing (Josserand and Gallavardin¹⁹), there is much scar tissue. In every case three points are noted: (1) the lymphocytes and the mononuclear phagocytes are the prominent cells; (2) the infiltration is primarily in the interstitial tissue; (3) neither cultures nor specially stained slides have ever revealed any bacteria or spirochetes, with the single exception of Rindfleisch's case¹ which we have ruled out of our discussion.

The other organs show acute passive congestion in 19 cases. Occasionally only the lungs show it. There are also many infarcts in the cases having mural thrombi. In several cases foci of infection were revealed, in addition to the cases where infection could be noted clinically. They are: The case of Josserand and Gallavardin¹⁹ in which there was tuberculosis of the axillary lymph nodes; Freund's case,³ in which a macerated *Tania solium* was recovered from the intestine and cysticerci were found on the cerebral cortex; Fiebach's first case¹³ in which there were chronic nephritis and cholelithiasis: his second case in which there were abscesses in the right ear and an aortic lesion which was probably luetic; Gierke's case,⁸ in which the tonsils exuded pus and the pelvis contained a chronic infection; and Saltykow's case, in which were found caseous pulmonary tuberculosis and parenchymatous degeneration of the kidneys. In general, there were no frequently repeated lesions other than these in the heart, and the congestion and infarction subsequent to them; but there were pyogenic infections sometime in the course of eleven out of the thirty-two cases reported; something resembling grippe associated with the onset in three, and specific infections such as tuberculosis or gonorrhea in five.

SUMMARY

A case is reported in which the clinical picture simulated that seen in coronary occlusion, but the pathological findings were those of acute interstitial myocarditis. In a brief review of the literature the following points stand out:

1. The diagnosis is necessarily a pathological one, since there is no uniform clinical picture.
2. While sudden death sometimes occurs, in the majority of cases death is preceded by symptoms of progressive myocardial failure of variable duration.

3. Although there is no known etiology, the frequent association with infections, especially pyogenic infections of the skin, is suggestive.

4. Analysis of the pathological findings in thirty cases reveals the fact that the microscopic picture is the one constant finding.

5. In the majority of the cases there are also cardiac hypertrophy and dilatation, a greyish-yellow mottling of the myocardium of the left or both ventricles, and acute congestion of the viscera.

6. In most of the cases of more than one month's duration there are mural thrombi in the left ventricle.

REFERENCES

1. Fiedler, A.: Ueber akute interstitielle Myokarditis, Festschrift z. Feier d. fünfzigjährigen Bestehens d. Stadtkrankenhauses zu Dresden-Friedrichstadt, 1899, Dresden.
2. Steffen, A.: Zur akuten Myokarditis, *Jahrb. f. Kinderheilk.*, 27: 223, 1888.
3. Freund, G.: Zur Kenntniss der akuten, diffusen Myokarditis, *Berl. klin. Wehnschr.*, 35: 1077, 1106, 1898.
4. Rindfleisch, W.: Ein Fall von diffuser akuter Myokarditis, Inaugural-Dissertation, München, 1896.
5. Wolf, Franz: Ein Fall von Myokarditis acuta bei gleichzeitig bestehender Hypertrophie und Dilatation des Herzens, Inaugural-Dissertation, München, 1896.
6. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, *AM. HEART J.*, 5: 129, 1929.
7. Baumgartner, H.: Ueber spezifische diffuse produktive Myokarditis, Frankfurt. *Ztschr. f. Path.*, 18: 91, 1916.
8. v. Gierke, E.: Ueber granulierend-productive Myokarditis mit Regeneration von Herzmuskelfasern, *Beitr. z. path. Anat. u. z. allg. Path.*, 69: 72, 1921.
9. Saltykow, S.: Ueber diffuse Myokarditis, *Virchows Arch. f. path. Anat.*, 182: 1, 1905.
10. Zuppinger: Ueber Herztod bei anscheinend bedeutungslosen oberflächlichen Geschwürs-processen, *Wien. klin. Wehnschr.*, 14: 799, 1901.
11. Lemke, R.: Zur Frage der primären akuten und parenchymatösen Myokarditis, *Virchows Arch. f. path. Anat.*, 248: 345, 1924.
12. Schminke, M.: Isolierte, akute, diffuse, interstitielle Myokarditis, *Deutsche med. Wehnschr.*, 47: 1047, 1921.
13. Fiebach, R.: Ueber isolierte diffuse akute interstitielle Myokarditis, *Virchows Arch. f. path. Anat.*, 233: 57, 1921.
14. Stolz, E.: Ueber die Aetiologie und die Folgen der isolierten diffusen interstitielle Myokarditis, *Zentralbl. f. Herz- u. Gefäßskr.*, 15: 183, 1923.
15. Kaufmann, E.: Lehrbuch der speziellen path. Anat., Berlin-Leipzig, 1922.
16. Sellentin, L.: Akute isolierte interstitielle Myokarditis, *Ztschr. f. klin. Med.*, 54: 298, 1904.
17. Hafner, A.: Ueber akute, diffuse, interstitielle Myokarditis, *Deutsches Arch. f. klin. Med.*, 138: 236, 1922.
18. Pal, J.: Akute, isolierte, interstitielle Herzmuskelentzündung, *Wien. med. Wehnschr.*, 66: 979, 1916.
19. Josseland, E., and Gallavardin, L.: De L'Asystolie Progressive des Jeunes Sujets par Myocardite Subaigue Primitive, *Arch. Gen. d. Méd.*, 78: 513, 684, 1901.
20. Cohn, L.: Ueber diffuse subakute Myocarditis, Inaugural-Dissertation, Heidelberg, 1915.
21. Schilling: Zwei Fälle von akuter, idiopathischer Myokarditis mit Zahlreichen Riesenzellen, *Verhandl. d. deutsch. path. Gesellseh.*, 18: 227, 1921.
22. Mordre, S.: Acute Interstitial Myocarditis, *Norsk Mag. f. Laegevidensk.*, 85: 722, 1924.
23. Förster, F.: Ueber Myokarditis und Gefässerkrankungen im Kindesalter, insbesondere nach akuten Infektionskrankheiten, *Deutsches Arch. f. klin. Med.*, 85: 35, 1905.

CALCAREOUS AORTIC VALVULAR DISEASE^c

HARRY M. MARGOLIS, M.D., FREDERICK O. ZIEMLIESSEN, M.D., AND
ARLIE R. BARNES, M.D.
ROCHESTER, MINN.

THE etiology of a markedly calcareous, frequently stenotic valvular lesion confined almost entirely to the leaflets of the aortic valve is puzzling to the pathologist. Occasionally this lesion is so striking, in contrast with total lack of any other signs of disease of the cardiovascular system, that the etiological factor seems hopelessly concealed. From the clinical standpoint, too, this condition sometimes presents incongruities. There may be marked incompetence of the valve, considerable stenosis, and evidence of valvular disease of long duration, but absence of symptoms of cardiac disease. Not infrequently the lesion found at post-mortem examination has been entirely unsuspected. The lack of clinical awareness of the existence of this condition can be accounted for, in large measure, by the scanty attention that the subject has received in the medical literature of recent years.

A study of the clinical course of this disease and of its pathogenesis, and an attempt to elucidate its etiology seemed indicated. Therefore thorough clinical and pathological investigations of the condition were undertaken.

In view of the fact that the lesion of the aortic valve in such cases is probably one of long standing, it appeared that evidence of its pathogenesis may have been hidden by the extensive calcification which occurs. Hence, it seemed necessary to construct a conception of the probable pathological process by thorough analysis of the clinical data as well as by pathological studies. This was attempted by means of a review of the clinical and pathological records and by gross and histopathological studies of the heart, including histological studies of the myocardium, of the aortic valves and occasionally of the mitral valves, and of the arch of the aorta.

REVIEW OF LITERATURE

From a view of the clinical data and the pathological specimens of twenty-eight cases of "pure aortic disease," Cabot² concluded that these cases of solitary aortic stenosis are related etiologically to rheumatic endocarditis. This conclusion was arrived at despite certain important facts which the author admitted militated against this hypothesis. Cabot pointed out that in his series of twenty-eight cases of pure aortic disease, only three occurred in females and twenty-five in

^cFrom The Mayo Clinic.

males. The age incidence of these lesions was also strikingly different from that encountered in apparently proved cases of rheumatic carditis, for only six patients of this series were less than forty years old and half the patients were more than fifty years old when they were first seen. "Such an incidence as regards age and sex," stated Cabot, "contrasting strongly as it does with that of the recognized rheumatic cases, cannot help making us suspect at once that these cases belong to a separate group, and are very possibly of a different etiology." Yet in this series of cases a history of rheumatic fever, chorea, or tonsillitis was about as frequent as in the group of cases designated rheumatic.

Cabot could not find evidence of syphilis as a cause of the lesion. Neither could he find unequivocal evidence for an arteriosclerotic basis of the affection. He was impressed by the similarity of the pathological pictures in the valves in the cases of pure aortic stenosis and in those of juvenile rheumatic endocarditis and laid great stress on the occurrence of acute aortic endocarditis in several cases of pure aortic disease, assuming that the acute process is a recrudescence or relapse on the basis of a healed process of like type. What appeared to militate most strongly against the general hypothesis of arteriosclerosis for the whole group is the absence of arteriosclerosis in other parts of the circulatory system in twelve cases of the series.

In a study of the various types of valvular diseases of the heart, Clawson, Bell and Hartzell³ found fifteen hearts in which there was marked thickening and stiffening of the leaflets due to large calcareous nodules within them. The position of these nodules in no way corresponded to that of the vegetations of active endocarditis, although varying degrees of calcification were found to occur in valves which gave evidence of subacute bacterial endocarditis. The average age of the patients with aortic nodules was fifty-four and a half years. These investigators could not find satisfactory evidence in favor of inflammatory origin of these calcareous lesions in the fifteen hearts in which there was evidence of predominant calcareous aortic valvular disease. They asserted the belief that the calcified nodular type of old valvular defect may originate entirely independent of an inflammatory process, and concluded that the etiology of this type is unknown.

Mönckeberg⁸ concluded that calcification of the aortic valves is not the result of an inflammatory process, but rather the result of a degenerative process with secondary deposition of calcium.

Commenting on the possible mechanism of development of nonbacterial, chronic cardiovalvular disease, Thalheimer¹⁰ wrote: "Some general toxic or some distant infectious process might result in a primary trauma to a heart valve. . . . Thickening of the valve follows, and these thickened valves have been found to be free from bacteria. Thus, the process of valve thickening can be regarded as nonbacterial

in origin. . . . This may eventually produce a marked stenosis with a shelf-like formation at the line of valve closure." He then added: "Fibrosed, thickened and stenosed valves, found in general arteriosclerosis can be explained similarly. The unusual amount of calcareous deposit in these cases is undoubtedly part of the process of arteriosclerosis, probably initiating the valvular lesion and undoubtedly contributing markedly to its progression."

MATERIAL FOR STUDY

Altogether forty-two cases of calcareous endocarditis of the aortic valve were available for study. This represents a consecutive series of cases as they came to necropsy between the years 1922 and 1930, except for several cases in which the hearts were not available for study. These cases were selected on the basis of the existence, pathologically, of calcareous infiltration of the leaflets of the aortic valve, in the absence of significant degrees of involvement of other valves. Not infrequently, however, very small atheromatous plaques occurred within some of the leaflets of the mitral valve, or slight thickening of the leaflets of the mitral valve was observed. However, such pathological changes as occurred in the leaflets of the mitral valve may be disregarded in our present consideration, since such changes, in general, occurred not more frequently nor to any greater degree than may be observed in apparently normal hearts of persons of the ages corresponding to those of the patients in our series.

ANALYSIS OF CLINICAL DATA

It is significant that a history of "rheumatism" was elicited in only three cases, and in one other case recurrent attacks of chronic arthritis and myositis had occurred for a period of ten years. Tonsillitis occurred in five cases, influenza in thirteen cases, and scarlet fever in eight cases. In one case, in which there was a history of syphilitic infection eighteen years previously, there was no clinical evidence of this infection, and the Wassermann reaction of the blood was negative. In another case, the Wassermann reaction of the blood was strongly positive, but neither a history of the primary syphilitic lesion, nor signs of syphilis, could be elicited. In two other cases there was a history suggestive of syphilitic infection, of which definite confirmatory evidence was lacking.

Distribution by Sex and Age.—In the forty-two cases there were eight females and thirty-four males. With the exception of one patient, who was twenty-five years old, the ages of the patients when first seen at the clinic varied from thirty to eighty-seven years. As can be seen in Table I, only three patients were less than forty years old, and thirty-five patients were more than fifty years old when they presented themselves for the first examination. Seven patients were

examined at the clinic on more than one occasion, at intervals varying from four to eighteen years. Although the presenting complaint at the first examination in six of these cases was not referable to the heart, a record of the occurrence of persistent cardiac murmurs at the first examination in each instance, and subsequent finding of the valvular lesion indicate the probable existence of the cardiac lesion at the time of the first examination. One of these patients came primarily on account of indefinite precordial distress. This patient lived for eleven years thereafter and died of cardiac decompensation and paroxysmal tachycardia. One other patient, who was first seen at the

TABLE I
AGE AND SEX INCIDENCE

| AGE, YEARS | MALE | FEMALE |
|------------|------|--------|
| 25 | | 1 |
| 30 to 39 | 2 | |
| 40 to 49 | 3 | 1 |
| 50 to 59 | 6 | 3 |
| 60 to 69 | 11 | 3 |
| 70 to 79 | 8 | |
| 80 to 89 | 4 | |
| Total | 34 | 8 |

age of thirty years, on account of chronic arthritis, died suddenly ten years later, in an attack of cardiac decompensation. In the remaining five cases of this group death was primarily ascribed to conditions other than cardiac, and during life there were few symptoms attributable to the cardiac defect.

SYMPTOMS AND SIGNS

The most striking feature with regard to symptoms in this group of cases is lack of any characteristic complaints. Often symptoms referable to the cardiovascular system are not present. As may be seen in Table II, only six patients presented themselves for examination primarily on account of symptoms which were attributed directly to the heart. Two other patients complained of symptoms typical of angina pectoris, associated in one instance with frank hyperthyroidism and in the other with pernicious anemia. Haines and Kepler⁴ have pointed out the part played by hyperthyroidism in precipitating the syndrome of angina pectoris, and Willius and Giffin¹³ have observed a similar effect of pernicious anemia in certain cases. Both of these patients, however, were found to have considerable sclerosis of the coronary arteries, making it more likely that the anginal pain was due directly to this cause. In one instance, in which disease in the aortic valve was found at necropsy, the patient had not been under observation of physicians at the clinic and a detailed history was not available. When cardiac symptoms were noted by the patient, in general they ranged

from a complaint of slight dyspnea on exertion indicative of myocardial insufficiency, to symptoms resulting from a severe grade of cardiac decompensation.

As might be expected, dyspnea was the most common of the cardiovascular symptoms and was noted in twenty-one cases. Eight patients complained of palpitation; this symptom could be attributed to an associated condition, such as hyperthyroidism in several instances.

TABLE II
PRIMARY CONDITIONS FOR WHICH PATIENTS PRESENTED THEMSELVES FOR EXAMINATION

| CONDITION | CASES |
|--|-------|
| Myocardial decompensation | 4 |
| Myocardial decompensation and coronary sclerosis | 2 |
| Hypertrophy of prostate gland | 6 |
| Hyperthyroidism | 4 |
| Carcinoma of rectum | 4 |
| Carcinoma of bladder | 3 |
| Carcinoma of prostate gland | 1 |
| Carcinoma of esophagus | 1 |
| Carcinoma of thyroid gland | 1 |
| Carcinoma of breast | 1 |
| Exophthalmic goiter and angina pectoris | 1 |
| Empyema of gall bladder | 1 |
| Pernicious anemia and angina pectoris | 1 |
| Intestinal obstruction | 1 |
| Erysipelas | 1 |
| Tumor of brain | 3 |
| Cerebral arteriosclerosis | 1 |
| Cholecystitis with stones | 1 |
| Myeloma of sternum | 1 |
| Vesical calculus | 1 |
| Pneumonia | 1 |
| Epigastric hernia | 1 |
| No history | 1 |

Otherwise, patients who presented evidence of myocardial insufficiency had palpitation. Eight patients complained of weakness, but the majority of these had some concomitant condition which seemed to account for the complaint. Others had it in the presence of cardiac failure. Seven patients complained of slight cough, and two had had vertigo.

Four of the forty-two patients had preeordial pain. Two of these had pain typical of angina pectoris; it was precipitated by exertion and radiated to the left arm. Two other patients complained of substernal oppression or indefinite preeordial pain on exertion.

On general examination the patients usually were found to be fairly well nourished. There was not any particular tendency to obesity. When there was evidence of considerable loss of weight, this could be ascribed to some condition other than the cardiac defect.

Pallor was observed in three cases. In at least two of these it was not related to the cardiac condition. Cyanosis, which was observed in four cases, always was associated with a marked degree of cardiac

decompensation. Varying degrees of passive congestion were observed in thirteen cases. Usually this was manifest by only slight pitting edema of the ankles or by the presence of numerous moist râles at the bases of the lungs. Rarely massive edema occurred, and that always in association with other signs of marked decompensation.

Varying degrees of cardiac enlargement were noted clinically in twenty of the forty-two cases. In one case, the measurements of the area of cardiac dullness were within normal limits. Records of the size of the heart in the remaining cases were not available. The pulse rate ranged from 64 to 190 beats a minute. The highest pulse rate occurred in a case of paroxysmal tachycardia. Usually the pulse rate was within normal limits. When tachycardia existed, it usually was in a case in which some associated condition was present, such as hyperthyroidism, or some infectious process outside of the cardiovascular system. In several cases the tachycardia was associated with cardiac decompensation.

Auricular fibrillation occurred in seven cases. In three of these, frank hyperthyroidism existed. Premature contractions were observed in three cases. In the remainder, the pulse was of normal rhythm.

In twelve of the cases the systolic blood pressure recorded at the first examination ranged above 160 mm. of mercury. The highest readings recorded in two cases were 220 systolic and 70 diastolic, and 210 systolic and 98 diastolic. The presence of a Corrigan pulse was not noted in either of these two cases. Some of the cases in which relatively low readings of blood pressure were found presented evidence of myocardial insufficiency. In several cases the blood pressure, several months or several years prior to the last examination, revealed evidence of moderate hypertension, whereas at the time of the last examination the readings of blood pressure were distinctly lower. There was no clinical or pathological evidence of myocardial infarction in any of these cases, and the decline of the blood pressure was not necessarily associated with evidence of significant degrees of myocardial insufficiency.

In twenty-two of the forty-two cases there was clinical evidence of sclerosis of the palpable peripheral arteries. In the other cases, specific mention of the condition of the arteries was not made. Of the twenty-two cases of peripheral arteriosclerosis, the degree of sclerosis was graded slight in ten cases, moderate in five cases, and marked in two cases. The degree of sclerosis in the other five cases was not recorded.

It is remarkable how variable were the physical manifestations in the heart and how markedly the physical signs in these cases differed from those regarded as diagnostic of aortic stenosis or insufficiency. The cardiac murmurs varied both in situation and in character. In

nine cases, the murmur was heard over the entire precordium and was usually systolic, and loud or squeaking in character. In one of these cases both a presystolic and a systolic murmur were heard over the entire precordium. In six cases a loud or rough systolic apical murmur only was heard. This murmur was usually transmitted to the axilla only, or to the axilla and over the precordium. In seven other cases, systolic murmurs were heard over both the aortic and mitral areas. In two of these cases the murmurs were described as being musical; in one case the murmurs were soft and blowing. In three cases a roughened systolic murmur, varying greatly in intensity, was heard with maximal intensity over the aortic area and was transmitted upward to the vessels of the neck. The presence of a thrill was not recorded in any of these three cases. In one case a loud, diastolic murmur, heard best over the aortic area and transmitted down the sternum, was associated with a soft, blowing systolic, apical murmur. In another case, a rough systolic and a faint diastolic murmur were heard over the aortic area, associated with a systolic apical murmur. In still another case, to-and-fro aortic and apical murmurs were heard. Murmurs occurring in two other cases were insufficiently described. In twelve cases there was no record of a murmur having been heard.

In two cases in which the occurrence of a thrill was mentioned, it was felt over the region of the apex.

The second aortic sound was recorded as being absent in one case, and paradoxically, accentuation of the aortic second sound was heard in three cases. In one of these there was stenosis of the aortic valve due to a marked degree of calcification of the leaflets. In the two other cases, the degree of calcification was relatively slight.

Electrocardiographic records were available in seventeen cases. In general, significant abnormalities in the electrocardiogram were comparatively uncommon. Inversion of the T-wave in Lead I alone occurred in three cases; in Leads I and II in one case; in Leads II and III in one case, and in Lead III alone in three cases. Left ventricular preponderance was noted in nine cases, and right ventricular preponderance in four cases. Auricular flutter and ventricular premature contractions were noted in one case. Incomplete bundle-branch block with prolongation of the QRS interval to 0.13 second was observed in one case. Notching of the QRS complex in isolated or multiple derivations was noted in several instances.

Roentgenograms of the thorax were available in twenty-eight cases and usually confirmed the clinical impressions regarding the increase in the size of the heart. In three cases the roentgenogram revealed regions of calcification in the arch of the aorta. Marked torsion of the arch of the aorta was reported in two cases, and dilatation of the arch of the aorta in two cases.

Records of examinations of the ocular fundi were available in fifteen cases. Sclerosis of the retinal arteries, of mild or moderate degree, was observed in four cases. In one case the fundus revealed only mild retinal arteriosclerosis of the senile type. In two cases, in which there was evidence of tumor of the brain, the fundus revealed choked disks. In the remaining eight cases the fundi were essentially normal.

Other indications of arteriosclerosis were the occasional presence of clinical evidence of cerebral arteriosclerosis, or roentgenologic evidence of calcification in the peripheral arteries in the legs.

A clinical diagnosis of cardiovalvular disease was made in only seven cases. Among these, aortic stenosis was diagnosed in only two cases. This was suspected clinically as being on an arteriosclerotic basis. The clinical diagnosis in these seven cases was as follows: aortic sclerosis and mitral regurgitation(?); mitral regurgitation; chronic mitral endocarditis with stenosis (one year later in the same case a diagnosis was made of coronary and aortic sclerosis with paroxysmal tachycardia and congestive failure); probably aortic regurgitation, the diagnosis being changed ten years later to rheumatic mitral stenosis and insufficiency; aortic stenosis; aortic stenosis and insufficiency and mitral insufficiency, and suspicion of mitral insufficiency. A diagnosis of aortic sclerosis was made in two cases. In the other cases, the existence of valvular disease was not suspected.

A review of the primary causes of death in these cases also brings out rather surprising facts. Although the pathological appearance of the cardiac lesion gives evidence of long duration of the process, death that could be ascribed primarily to the cardiac lesion was infrequent. Table III shows that in only ten cases was death due to cardiac decompensation, and in one of these cases the cardiac decompensation was associated with generalized sepsis. In five other cases death occurred suddenly. In three of these cases considerable sclerosis of the coronary arteries was found, without evidence of occlusion, however; in

TABLE III
MODE OR PRIMARY CAUSE OF DEATH

| CAUSE OF DEATH | CASES |
|---|-------|
| Myocardial decompensation | 9 |
| Myocardial decompensation with sepsis | 1 |
| Sudden death | 5 |
| Uremia and pyelonephritis | 9 |
| Pneumonia | 5 |
| Pulmonary embolism | 2 |
| Emaciation | 2 |
| Postoperative shock | 2 |
| Gastric ulcer and hemorrhage | 1 |
| Edema of glottis | 1 |
| Peritonitis | 1 |
| Respiratory failure (cerebral tumor and fracture of cervical spine) | 2 |
| Mesenteric thrombosis | 1 |
| Carcinoma of pancreas | 1 |

one case there was severe cardiac decompensation. The fifth case in which sudden death occurred was that of a woman, suffering from exophthalmic goiter associated with auricular fibrillation and congestive cardiac failure. At necropsy the coronary arteries were found not to be sclerosed, but there was stenosis of the aortic valve due to fusion and calcification of the right and left anterior aortic cusps. Death in the remaining cases of our series was due to various causes not directly attributable to the heart.

ANALYSIS OF PATHOLOGICAL DATA

Weight of the Heart.—As may be noted in Table IV, the weights of the hearts varied markedly. In some cases the heart weighed less than 300 gm. whereas in others it exceeded 500 gm. In one case, the heart weighed 740 gm. It is difficult to determine with accuracy the factors that played the greatest part in causing the degree of cardiac hypertrophy. Excluding such factors as the variations in body weight and in the age of the patients, factors which could not by themselves effect such wide variations in the size of heart, we have left several other factors which must be considered. Marked variations in the blood pressure, although not a striking feature when the patients were seen at the clinic, might have played an important part in previous years. Undoubtedly the presence of insufficiency, stenosis, or of both insufficiency and stenosis of the aortic valve was responsible in most cases for the marked ventricular hypertrophy, but the existence of valvular insufficiency or stenosis was not always apparent at necropsy when it probably existed during life. It seems most probable that a combination of various factors is the cause of the variable degree of hypertrophy which occurs in these hearts.

Pericardium.—One case of typical calcareous aortic valvular disease was associated with adhesive pericarditis which had entirely obliterated the pericardial sac. Evidence of pericarditis was not seen in the other hearts of the series. In seventeen cases the pericardial cavity contained an excess of clear, straw-colored fluid which ranged in

TABLE IV
WEIGHTS OF HEARTS IN GRAMS

| 200 TO 299 | 300 TO 399 | 400 TO 499 | 500 TO 599 | 600 TO 699 | 700 TO 799 |
|------------|------------|------------|------------|------------|------------|
| 265 | 308 | 428 | 550 | 675 | 740 |
| 283 | 328 | 420 | 500 | 685 | |
| 205 | 370 | 480 | 500 | | |
| 230 | 365 | 435 | 543 | | |
| 275 | 360 | 450 | 530 | | |
| | 384 | 402 | 504 | | |
| | 380 | 443 | 565 | | |
| | 367 | 410 | 514 | | |
| | 370 | 442 | 509 | | |
| | 313 | 483 | 595 | | |
| | 322 | 415 | | | |
| | 300 | 410 | | | |

amount from 20 to 200 c.c. In twenty-one cases there was no excess fluid, and in four cases the quantity of pericardial fluid was not recorded.

Cardiac Valves.—In the mitral, tricuspid and pulmonary valves there were no significant pathological features. We have already referred to the slight atheromatous changes observed occasionally in the mitral valve.



Fig. 1.—Superior surface of aortic valve. Irregular nodular infiltration with calcareous material, producing distortion of valve and stenosis (natural size) is shown.



Fig. 2.—Cross-section of aortic valve leaflet. Marked calcareous deposition within the valve leaflet is shown, the calcareous nodule being covered by endothelium.

Only the aortic valve presented the significant and solitary valvular defect, which was characterized in general by a variable amount of calcareous deposition within the valve leaflets producing distortion and stiffening of the valves and, in certain instances, varying degrees of stenosis, insufficiency, or both. A characteristic feature of the process was the involvement primarily of the aortic ring, frequently of one of the commissures, and, in more markedly involved valves, ex-

tension of the pathological process onto the valve leaflets (Fig. 1). Rarely did the calcified deposits extend quite to the free margin of the valve leaflets, unless the process was extremely marked. The areas of calcification appeared as whitish, or grayish-white nodules, each with an irregular outline and surface, although at times the surface was smooth. In the milder degrees of involvement, palpation of the aortic



Fig. 3.—Fusion of the right and left anterior cusps of the aortic valve by infiltration with calcareous material.

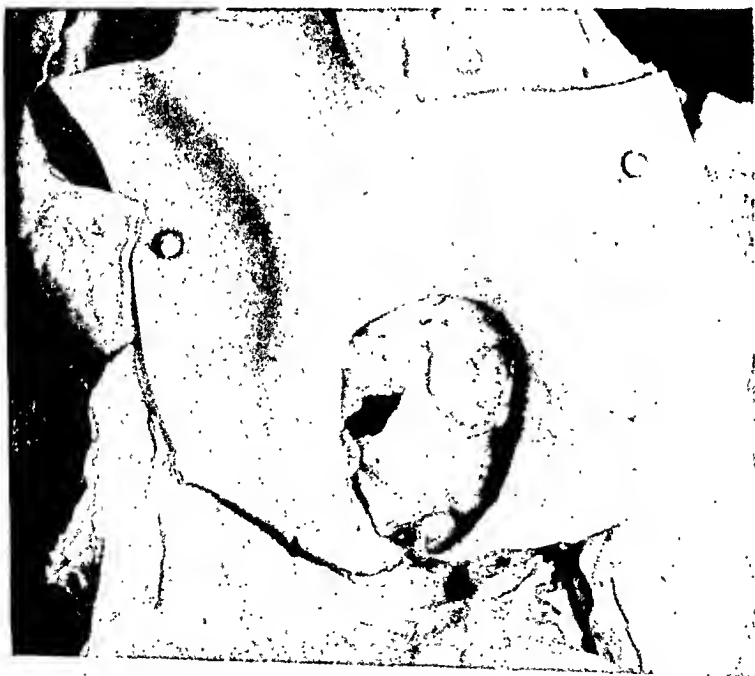


Fig. 4.—Marked degree of calcareous infiltration in aortic valve, producing fusion of all cusps and marked stenosis.

margin revealed a firm, irregular, calcareous ring with spicules of calcium projecting onto the aortic surface of the attached border of the valve leaflets. Several small, calcified nodules might also be felt scattered on the aortic surface of the cusps nearer the ring than the free margin. These nodules appeared to be completely covered by endothelium, which, except for its irregular contour, contained noth-

ing of note (Fig. 2). Frequently fusion of the edges of the cusps was found. In twenty of the forty-two hearts examined, this fusion involved the adjacent edges of the right and left anterior cusps (Fig. 3). In five of these cases, fusion of the cusps was not complete, the process extending from the commissure for a distance of a third or a half of the width of the edge of the cusp. At times this fusion was due only to fibrous tissue, but usually there was found deposition of a variable amount of calcium, which, when abundant, seemed to creep into the adjacent portions of the cusps and to extend beneath the endothelial points on the aortic surface of the cusps. The remainder of the valve might appear entirely normal, or a variable degree of thickening and stiffening might be present. In five hearts, the deposition of calcium occurred between the edges of the right anterior and the posterior cusps, producing partial or complete fusion between them. In two cases in which the process of calcification was extensive, all cusps were fused and were infiltrated with large amounts of calcium, thus forming a rigid diaphragm in which there was a small irregular opening through which the blood entered the aorta (Fig. 4).

The gross appearance of the valves with the less extensive degree of calcification revealed the process to be confined to the subendothelial layers of the valve. The calcium was irregularly distributed, and the process must have begun nearer the aortic than the ventricular surface of the valve, for in earlier stages, when the masses of calcium were still very small, they projected onto the aortic surface of the valve rather than onto the ventricular aspect. The inferior surface of the valve was, in fact, perfectly smooth and regular, whereas the aortic aspect presented an irregularly nodular appearance. The endothelium appeared to be intact, and no vegetations or thrombi were to be found.

In the more severe grades of involvement the nodules of calcium were larger and more numerous, and were spread irregularly on the surface of the aortic valve. When the extent of the process was marked, nodules of calcium might also appear on the ventricular surface of the valve. Even with fairly extensive infiltration of the cusps with calcium it might, however, often be seen that the process still remained confined to the subendothelial tissue. However, not infrequently, there was ulceration of the surface endothelium over the most prominent nodular areas of such valves. The areas between the nodules might appear normal or might be somewhat thickened.

Occasionally the infiltration with calcium extended from the aortic ring onto the immediately adjacent portions of the aorta. The process was never observed to extend far enough onto the aorta to involve the orifices of the coronary arteries.

The degree of stenosis or insufficiency which resulted from this process in the aortic valve could not always be estimated from the examination of the pathological specimen. In at least twenty-two

hearts the stiffening of the leaflets of the valves was such as to make it appear that a variable degree of stenosis must have existed, and in at least seven hearts the extensive stiffening and calcification of the valves undoubtedly produced both stenosis and insufficiency. How often insufficiency alone existed, it was more difficult to estimate. When all three cusps were involved, and were transformed into a rigid diaphragm, the valvular opening might be extremely small, measuring in some cases only 4 mm. in diameter.

In five hearts the process of calcification extended beyond the aortic valve into the ring of the mitral valve. When the mitral ring was involved, the process was either confined to the line of attachment of the aortic leaflet of the mitral valve or the degree of involvement was most pronounced in that part of the ring, fading off in degree in the remainder of the valve ring. In six other hearts the deposition of calcium involved not only portions of the mitral ring, but extended



Fig. 5.—Extension of calcareous process from posterior aortic valve leaflet onto mitral ring and ventricular surface of the anterior aortic leaflet of mitral valve; the calcareous material is seen as two finger-like processes extending from the base of the aortic leaflet.

for a short distance onto the ventricular surface of the aortic leaflet of the mitral valve (Fig. 5). Calcification of the mitral leaflet, however, usually was of slight degree and did not interfere with the function of the valve. Even when areas of calcification did exist in the mitral leaflet, there was no evidence of any other defect in the mitral valve. The auricular surface of the mitral valve was always found to be normal; there was no evidence of preexisting endocarditis.

The coronary arteries in all instances, except one, revealed some degree of sclerosis. In fifteen cases the sclerosis in the coronary vessels was slight; in fifteen cases, moderate; in nine cases, marked, and in two cases, extreme. Occlusion of any of the larger branches of the coronary vessels was not found.

The aorta, too, presented a variable degree of arteriosclerosis. It was slight in thirteen cases, moderate in twelve cases, marked in fif-

teen cases, and extreme in two cases. In general, the sclerosis in the aorta was least pronounced in its proximal portion.

Gross examination of the myocardium revealed scattered areas of grayish streaking due to myocardial fibrosis in fourteen cases. The extent of fibrosis varied considerably and was pronounced in several cases. Evidence of gross myocardial infarction was not encountered. Accumulations of fluid in the pleural sacs were found in ten cases. The fluid was always clear and straw-colored, and varied in amount from 1000 to 3000 c.c. There was marked passive congestion of the liver in three cases, atrophy of the parenchyma in five cases, fatty changes in one case, and varying degrees of fibrosis in two cases. The kidneys presented variable degrees of atrophy in six cases, with well-marked sclerosis of the renal vessels in three cases, and infarcts in only one case. In the spleen, evidence of infarction was noted in one case, and marked congestion was noted in two cases.

Three cases were studied bacteriologically. In one case the culture was sterile. Hemolytic streptococci were recovered at necropsy in a case in which the patient died following amputation of a breast. In another case in which the patient died following exploration of a glioma of the brain, *Streptococcus viridans* was recovered from the blood at necropsy.

Microscopic Studies.—Sections were taken in each case from: (1) the interventricular septum, just below the aortic valve; (2) the left auricle, just above the mitral valve; (3) the aortic valve, including the valve ring; and (4) the root of the aorta. The sections were stained with hematoxylin and eosin, and a number of sections of the valves were stained for fat with Scharlach red. Although difficulty was experienced in cutting some of the sections of valves, decalcification was not necessary; an old microtome knife was used, and satisfactory preparations were made.

Sections of the interventricular septum and of the auricular muscle revealed, as the most prominent feature, hypertrophic changes in the muscle fibers. Occasionally increase in the amount of interstitial tissue was found, but this was never marked. Varying degrees of sclerosis of the myocardial vessels were noted in most sections. In one case there was marked sclerosis and calcification of one of the branches of the coronary artery, leading to almost complete occlusion of the lumen. Aschoff bodies were not found. With the exception of one case, cellular infiltration indicative of an inflammatory reaction was not encountered.

Sections of the root of the aorta usually revealed only pathological changes such as are to be found in any group of cases in which the ages correspond to those in our series. Thus, there occurred some

increase in the connective tissue in the media, with hyalinization, and in some instances evidence of arteriosclerosis and deposits of calcareous material.

In eight cases, sections of the proximal portion of the arch of the aorta revealed varying degrees of cellular infiltration. In four of these cases the degree of infiltration was extremely slight, consisting of small, focal collections of lymphocytes, endothelial leucocytes, and an occasional plasma cell. These collections of cells occurred only in the adventitia and usually surrounded small capillaries or were in close proximity to them. The smaller blood vessels in the adventitia of these aortas revealed proliferation of the endothelium, which in some cases resulted in almost complete obliteration of the lumen. The larger arterioles presented thickening of the wall by fibrous tissue. The aorta in another case revealed several small foci of perivascular infiltration, and associated infiltration in the aortic valve was found. This cellular exudate was situated in the fibrous valve ring and was composed of a fairly dense collection of cells, predominantly lymphocytes, an occasional plasma cell, and an occasional endothelial leucocyte. These cells were collected about the capillaries and were also spread diffusely throughout the tissue of the valve ring. Endothelial proliferation in the capillaries, within this valve ring, was a prominent feature. Within the aortic valve, near its base, there was a large, irregular mass of calcareous material which was, however, separated from the exudative cellular infiltration in the valve ring, by a narrow rim of partially hyalinized fibrous tissue which represented the base of the cusp. Old, practically acellular, and somewhat hyalinized fibrous tissue, surrounded the entire mass of calcareous material, so that nowhere did it extend onto the surfaces of the valve. A section of the myocardium, in this case, did not present evidence of an inflammatory reaction. The perivascular distribution of the cellular exudate, and the proliferative endothelial reaction within the capillaries, both in the valve ring and in the adventitia of the aorta in this case, was extremely suggestive of the pathological reaction to syphilitic infection. In a review of the clinical record in this case it was noted that there existed a suspicion of previous syphilitic infection, but this could not be confirmed. The patient also gave a history of recurrent attacks of "rheumatism." From the evidence at hand we look on the histopathological pictures in the aorta and in the aortic valve ring in this case as probably due to syphilis. In the other cases in which small focal collections of cells occurred in the aorta, sections of the valves and of the myocardium did not present evidence of an inflammatory reaction.

In the remaining three of the eight cases in which infiltration was noted in the aorta, the degree of this inflammatory reaction was pronounced. In one of these three cases the cells were closely aggre-

gated in one section of the adventitia. There were, in addition, scattered through the adventitia, a smaller number of small lymphocytes and an occasional endothelial leucocyte. Endothelial proliferation of capillaries was not observed in this section. Sections of the aortic

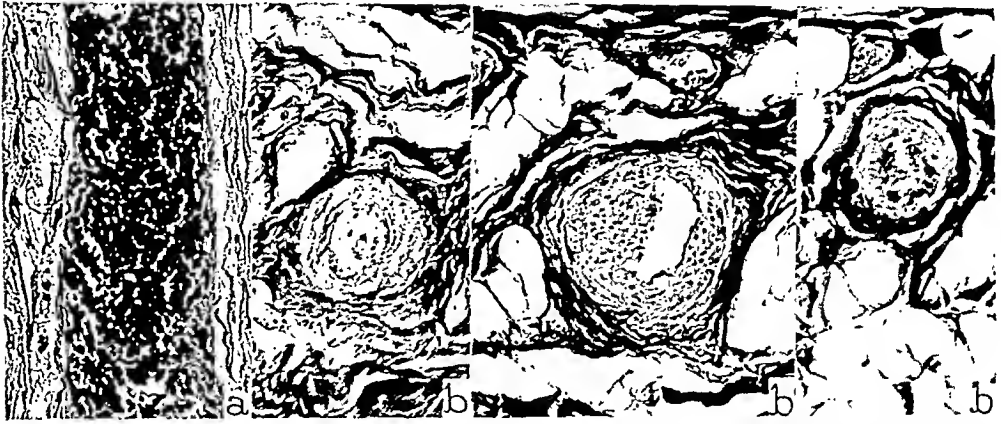


Fig. 6.—(a) Proximal portion of aorta, in a case of calcareous aortic valvular disease; perivascular round-cell infiltration in the adventitia (hematoxylin and eosin $\times 185$); (b) intimal proliferation in the vasa vasorum within the adventitia (van Gieson's stain $\times 175$).

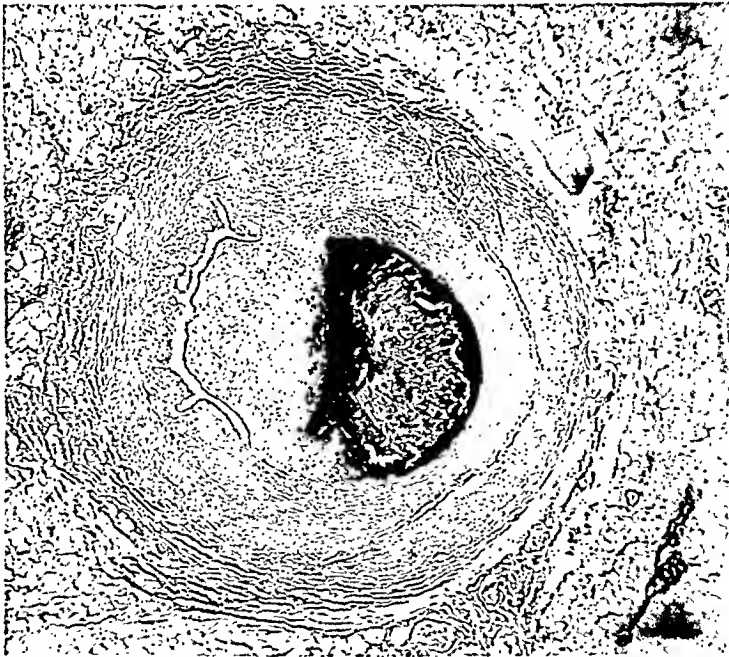


Fig. 7.—Marked intimal proliferation with thickening of the wall and narrowing of the lumen of one of the arteries within the adventitia of the aorta; also calcareous infiltration within the arterial wall and canalization (hematoxylin and eosin $\times 30$).

valve and of the myocardium did not reveal evidence of inflammatory reaction; neither was there a clinical history of rheumatic fever or of syphilis. In another case diffuse and perivascular lymphocytic infiltration in the adventitia and endothelial proliferation in the capillaries were associated with perivascular lymphocytes in the

media, which also showed scattered areas of degeneration. The microscopic appearance was extremely suggestive of syphilitic aortitis. This occurred in a case in which a strongly positive Wassermann reaction was found without other clinical evidence of the infection. In this case, too, the syphilitic nature of the aortitis hardly can be doubted. The myocardium revealed no evidence of an inflammatory reaction.

The third case in which pronounced infiltration of the aorta was noted was that of a woman aged twenty-five years, who did not give a history either of syphilis or of rheumatic fever, and who died of a brain tumor. There was marked lymphocytic perivascular infiltration in the adventitia of the aorta, and a pronounced degree of endarteritis

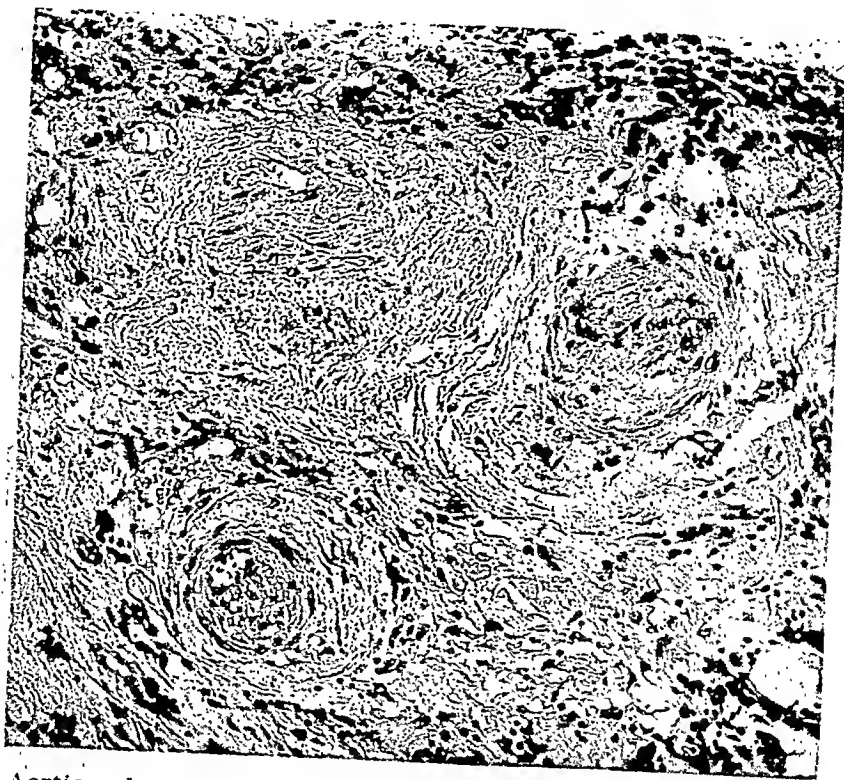


Fig. 8.—Aortic valve ring in a case of calcareous aortic valvular disease; marked endarteritis with tendency to obliteration of the lumina of the capillaries and beginning hyalinization of the surrounding connective tissue (hematoxylin and cosin $\times 125$).

of the smaller vasa vasorum, leading to complete obliteration of the lumina of many of them (Fig. 6). In one of the larger arteries within the adventitia of the aorta, at the level of the insertion of one of the aortic cusps, there was a most marked degree of intimal proliferation, which resulted in marked thickening of the wall of the artery, and encroachment on the lumen of the vessel; the lumen was reduced to a narrow slit only. The tissue of this thickened arterial wall had lost its cellular character and had assumed a hyalinized appearance. Within this thickened wall, on one side, there was a mass of calcareous material, and peripheral to it several narrow channels which appeared to be evidence of canalization within the thickened intima. There was no evidence of inflammatory reaction about this artery (Fig. 7). Sec-

tion of the aortic valve in this case revealed also pronounced inflammatory reaction within the valve ring. Endothelial proliferation of the smaller vessels in the valve ring was extremely pronounced; the lumina of many of the capillaries were almost completely obliterated by endothelium (Fig. 8). In the surrounding fibrous tissue there were advanced degeneration of the fixed cells; diffuse, but scanty, infiltration of lymphocytes, plasma cells, and endothelial leucocytes, and, in foci, proliferation of the fixed connective tissue cells. Irregularly distributed within the valve cusp, near its base only, were many irregular masses of calcareous material which lay embedded in almost acellular, homogeneously hyalinized connective tissue. It was rather striking to observe a zone of hyalinized connective tissue constituting the base

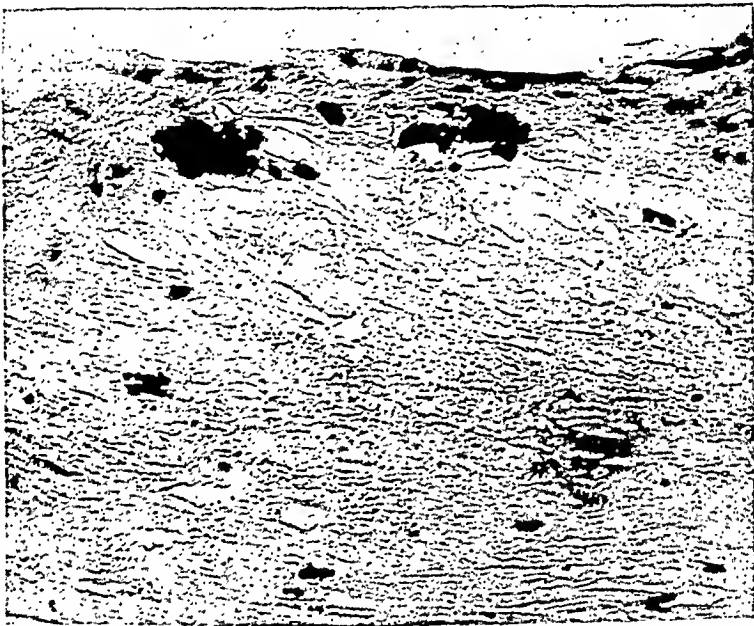


Fig. 9.—Cross-section of aortic valve leaflet: calcareous material deposited within the subendothelial and hyalinized connective tissue near the aortic surface of the cusp; cellular infiltration is absent (hematoxylin and eosin $\times 225$).

of the valve, separating the seat of the inflammatory reaction in the valve ring from the masses of calcareous infiltration in the valve cusp. We were impressed also by the relatively acellular appearance of the entire valve cusp, of which the thickened fibrous tissue throughout was the site of advanced hyaline degeneration.

Sections of the aortic valves revealed deposition of calcareous material, varying in degree from only small, dust-like, calcareous particles, to massive, nodular infiltration with calcium salts. Where only small amounts of calcareous infiltration were found, they were characteristically in the subendothelial connective tissue, near the aortic surface of the valve leaflet (Fig. 9). The endothelium appeared to be intact, and maintained its regular outline. With more marked degrees of infiltration, there was invasion of the middle layer of fibrous tissue in

the valve leaflet and subsequently extension of the process very near the aortic surface of the cusp. This produced bulging on the aortic surface, distorting the regular outline of the surface endothelium, but often leaving it intact (Figs. 10 and 11). Only in those cases in which extremely massive calcareous infiltration occurred was destruction of the surface endothelium found; the calcareous nodules were covered



Fig. 11.—Section through an area of calcareous infiltration within a leaflet of an aortic valve; calcareous deposition within the upper portion of the middle zone of cell hyalinized connective tissue and beginning destruction of endothelial covering; cellula infiltration is absent (hematoxylin and eosin $\times 223$).

by thin layers of fibrin. Surrounding the masses of calcareous material, was the thickened fibrous tissue of the valve, which was practically acellular and in many cases hyalinized. Scattered within the fibrous tissue, and particularly in the periphery of calcareous nodules, there were variable amounts of lipoid material which in foci formed rather large globules. Usually there was complete absence of cellular

infiltration in the affected valves; evidence of inflammation was entirely absent. However, in five of the forty-two cases, sections of the aortic valve revealed small collections of lymphocytes and endothelial leucocytes in the valve cusps, usually in the base of the valve, in the proximity of regions of calcareous infiltration. In one of these sections there was in the midst of the lymphocytes one giant cell. A section of the aortic valve in one case revealed ulceration of the endothelium near one of the calcareous nodules, and the presence of a small, partially organized vegetation in which there were still numerous lymphocytes and occasional polymorphonuclear leucocytes.

In view of the observation of striking obliterative vascular changes in the aortic valve rings in two of our cases, we directed further attention to the study of these rings in a number of cases with the view



Fig. 12.—(a) Section of aortic valve ring in a case of calcareous aortic valvular disease; thickening of the walls of arterioles and narrowing of their lumina (van Gieson's stain $\times 150$); (b) and (c), thickening of the walls of arterioles within the aortic valve rings in two other cases of calcareous aortic valvular disease (van Gieson's stain $\times 100$ and hematoxylin and eosin $\times 215$, respectively).

of determining the possible relationship of endarteritis in the vessels of the valve ring to the pathological changes in the valve. These sections of the valve rings were stained by hematoxylin and eosin, by the van Gieson method and by the Weigert elastic tissue stain. Of the sixteen cases studied from this standpoint, only a small number showed any striking vascular changes. Not in any case could we observe vascular changes as pronounced as those noted in the case which attracted our attention to this phenomenon, the case we have already described in detail. However, in four cases there was pronounced thickening of the walls of the smaller arterioles and proportionate narrowing of their lumina (Fig. 12). Changes in the intima were usually not marked, the thickening apparently resulting mainly from pro-

liferation in the media. Occasionally we observed endarteritis of the capillaries associated with arteriosclerotic changes in the arterioles. In one case, the fibrous tissue of the valve ring was hyalinized and almost avascular, but there were present whorl-like masses of poorly staining, flattened cells, which did not present lumina, but nevertheless suggested the appearance of completely obliterated capillaries, although their identification as such, with certainty, was impossible. In other sections the valve ring contained fairly numerous, normal-appearing vascular channels, contrasting markedly with sections of the valve rings from other hearts in which the connective tissue was practically avascular. Although equivocal, these observations of the vascular changes in the valve rings merit consideration in a study of the pathogenesis of this form of valvular disease.

It is interesting to consider why this lesion is so infrequently associated with signs of cardiac failure, even when it appears to have existed for a long time. First of all, the degree of stenosis and insufficiency of the aortic valve is probably relatively small except in the more advanced cases. The best evidence of that fact is the comparison of the relatively low cardiac weights encountered here with those found in cases of aortic stenosis and insufficiency due to other causes.

The left ventricle seems to have a large inherent capacity to compensate for the effects of aortic stenosis when compared with the reaction of the right ventricle to mitral stenosis. Willius found that patients with aortic stenosis survived, on the average, thirteen years longer than patients with mitral stenosis. It must be admitted, however, that mitral stenosis produces more widespread effect on the heart as a whole than does aortic stenosis.

When this group of patients is considered as a whole, there is little evidence that other factors coexist, leading to injury of the left ventricle. There is practically no evidence of myocarditis in the ventricles of these patients. The degree of coronary disease appears to be no greater than one would expect to encounter in a group of normal patients of the same sex and age. The number of patients in this group who had abnormally high blood pressures is small. In most cases the increase is chiefly in the systolic pressure, with relatively low diastolic readings, such as commonly are found in cases of hypertension associated with sclerosis and inelasticity of the aorta.

Finally, there are few disturbances of rhythm complicating these aortic lesions to interfere further with cardiac efficiency. Atrial fibrillation occurred in only seven cases, and in three of these hyperthyroidism was the probable cause.

The infrequency with which this condition of calcareous disease of the aortic valves was recognized clinically must depend in part on the fact that there are often few, and in some cases, no symptoms of cardiac disease associated with it. Obviously the first step in making

the diagnosis is the knowledge that such a lesion can exist and that it may be suspected especially in a patient who is more than fifty years old, and particularly if the patient is a man. This study indicates that the observations on physical examination will be those encountered in aortic stenosis or regurgitation from other causes. The murmurs heard in these cases usually are systolic in time, rough or musical in quality, maximal over the aortic region but having wide transmission over the precordium and to the vessels of the neck. If a painstaking attempt is made, it is believed that a thrill at the base of the heart can be demonstrated in a large proportion of these cases, and its demonstration fortifies the diagnosis greatly. In those cases in which regurgitation occurs, the usual diastolic murmur along the left side of the sternum will be heard.

From the standpoint of prognosis, these cases have both a favorable and an unfavorable aspect. On the favorable side is the fairly conclusive evidence that the lesion can exist over a long period without producing significant cardiac symptoms. On the unfavorable side is the fact that a certain proportion of the patients die suddenly; although until the time of death they appear to be in normal health. Certainly, in general, the prognosis in aortic stenosis of this type appears to be much more favorable than that of mitral stenosis.

COMMENT

On the basis of the pathological processes observed in the aortic valves involved by these peculiar calcareous deposits, one would be led to conclude that degenerative processes, probably on an arteriosclerotic basis, played an important and possibly a predominant part in the pathogenesis of this lesion. In support of this viewpoint must be mentioned the common occurrence of calcareous and hyaline degeneration of the valves and in some cases, the presence of obliterative vascular changes in the valve ring, in the absence usually of an inflammatory reaction. When the lesion is encountered at necropsy, the subject is usually a male more than fifty years old.

However, in a consideration of the etiology and pathogenesis of calcareous disease of the aortic valves, it is important to bear in mind that the lesions described here, in many cases, had begun many years before. It is obviously difficult to visualize, from pathological changes observed at the end of a disease process, the pathological process which occurred at its inception.

The possibility that this lesion may have an inflammatory basis receives some support from the observation of inflammatory processes in the aorta, in the aortic valve, or in both in eleven of our cases. This is particularly exemplified by one case which we described in detail, that of a woman twenty-five years old, who presented suggestive evidence of an inflammatory basis for typical calcareous aortic

valvulitis. In such a case, a rheumatic or other infectious etiologic basis for the affection must be strongly suspected, although the clinical history did not record episodes of infection. The death of this patient at an early age, and from a cause entirely independent of the cardiovascular lesion, may explain why an inflammatory process was still apparent in the affected valve and aorta at necropsy.

If it is assumed that this lesion has an infectious basis, then two possible mechanisms in its production are suggested by the observations made in this study.

1. It is possible that rheumatic fever may be the basis of many of the cases. According to this view, one assumes that this lesion begins as ordinary rheumatic aortic valvulitis and that the calcareous non-inflammatory lesion which is usually observed at necropsy represents a more or less completely healed lesion. This conception receives some support from a case of typical calcareous aortic valvular disease which came to necropsy since this study was completed. The patient, a man forty-five years old, gave a history of having had rheumatic fever and chorea at the age of twelve years, and he had had rather definite evidence of a valvular heart lesion at the age of twenty-five years, because of which he was refused life insurance. On clinical examination, the arterioles of the fundus oculi were normal. Only a negligible amount of sclerosis was observed in the coronary arteries and aorta at necropsy. It is difficult to evade the impression that there existed, in this case, an etiologic relationship between the rheumatic fever and the calcareous aortic valvular disease. If this process is accepted as being of rheumatic origin, then one must recognize that the distribution of the lesion in the valve is certainly unlike that usually observed in rheumatic valvulitis, particularly in respect to the freedom of involvement of the free margin of the cusps.

2. It is possible that this lesion results from an inflammatory process involving the arterioles of the aortic valve ring, leading to endarteritis in the nutrient arteries of the aortic valves, resulting in ischemia. This process is particularly suggested by the observations in the case of the woman twenty-five years old, which has been described.

Finally, it is possible that marked narrowing and possibly obliteration of the arterioles of the aortic valve ring, occurring as a part of ordinary generalized arteriosclerosis or as a selective, localized arteriosclerotic process might likewise produce ischemia of the aortic valves leading subsequently to degeneration of and calcareous deposits in the valves. According to this assumption the primary pathological changes in the valves would be due essentially to ischemia, possibly of insidious onset and of a slowly progressive character. This conception, too, might explain certain anatomical peculiarities of the pathological process such as the usual beginning of the process near the commissures of the valves, the more frequent fusion of certain valve

leaflets than of others, and the peculiar selective extension of the process in certain cases to the anterior (aortic) leaflet of the mitral valve, if there should exist certain peculiarities in the distribution of the vascular radicles of the blood supply to the aortic valve. Involvement of the *arteria anastomotica auricularis magna*, as described by Kugel, supplying branches to the aortic cusp of the mitral valve, occasionally to the aortic valve, to the commissures, and to the base of the aorta, might account for the pattern-like confinement of the pathological process to certain preferential regions; namely, the commissures, valve rings, and, in certain instances, the aortic cusp of the mitral valve. However, more detailed knowledge regarding the blood supply of the aortic valves is needed before one can determine their relation to the pathological process in the aortic valve described here.

In the development of the lesion any of these mechanisms, if they should prove to be correct, appear to satisfy certain conditions believed to permit the deposition of calcium, in that they are capable of initiating degenerative changes in the affected valve. We cannot enter here into a detailed consideration of the process of calcification, except to remark that aside from the pathological changes in tissues which make them suitable soil for the deposition of calcium, there probably exist certain chemical or physicochemical factors which either favor or impede the process. It is, however, well established that under certain pathological conditions calcification is likely to occur. Wells wrote: "It may be said that any area of dead tissue that is not infected, and that is so large or so situated that it cannot be absorbed, will probably become infiltrated with lime salts. Most frequently calcified, next to totally necrotic tissues, are masses of scar tissue that have become hyaline subsequent to the shutting off of circulation in the scar by contraction of the tissue about the vessels." With respect to the calcification which supervenes in the process of atherosclerosis of the aorta and other large vessels, the views expressed by Aschoff are probably most widely accepted. It must be recalled that as the fundamental pathological changes in that process Aschoff assumed the presence of a degenerative process of the supporting substance of the vessel wall, with subsequent processes of precipitation, especially of lipoid substances, and the subsequent transformation to calcium compounds. Although grossly, and in sections stained by hematoxylin and eosin, atheromatous changes in the valves are not recognizable, accumulation of lipoid material in association with hyalinization and calcification is nearly always evident when sections of the valves are appropriately stained for fat. Thus the appearance of the degenerative process in these valves and in atherosclerosis bear a close resemblance.

We can find no evidence to suggest that this process is the end-result of healed bacterial endocarditis, although we realize that healing in

bacterial endocarditis may result in varying degrees of calcification. In this connection, it is significant to observe the infrequency of a history suggestive of previous endocarditis, the absence usually of vegetative endocarditis, either active or healed, and the rare occurrence of infarction in the kidneys and spleen in these cases. Moreover, such a series of presumably completely healed lesions of bacterial endocarditis is not compatible with our present conception of this disease.

Despite the occurrence of histopathological data suggestive of syphilis in several of our cases, it is obviously impossible to suggest that syphilis frequently plays a part in the etiology of this form of valvular disease. Indeed, it is recognized that in the most commonly observed valvular lesions caused by syphilis, calcification is usually not a prominent feature.

The possibility that the valvular lesion is the result of thrombosis on the surface of the valve, with subsequent organization and calcification of the thrombus, suggests itself. However, in the earliest stages of the process, hyalinization of connective tissue, and calcification, occur characteristically within the substance of the aortic valve ring and in the connective tissue of the cusp beneath the endothelium which remains intact. It is only in the far advanced stages of the process, when the calcareous deposits become large, that they cause secondary changes in the endothelium, finally breaking it, the calcareous material then projecting on the surface of the valve.

More conclusive evidence bearing on the various mechanisms of pathogenesis considered here will probably come through studies of early cases, cases in which histories are complete and clinical observations have been made over long periods of time, and through a study of the degree and distribution of calcareous deposits in aortic valves associated with undoubted cases of rheumatic mitral endocarditis.

SUMMARY AND CONCLUSIONS

Although calcareous aortic valvular disease is relatively uncommon, it should be suspected more often when patients, particularly elderly men, present certain clinical phenomena which have been considered here. Heretofore, a clinical diagnosis of this condition rarely has been made. This is due to the tendency of the condition to cause few subjective symptoms, apparently the result of the remarkable capacity of the heart to compensate for the mechanical circulatory disturbance which this lesion produces. Lack of clinical awareness of this condition undoubtedly is a great factor tending to errors in diagnosis in this form of valvular disease.

Pathologically, the lesion is characterized by a tendency to hyalinization of the connective tissue, deposition of lipoid material in the aortic valve ring and in the aortic valve, and subsequent calcification of the affected tissues.

The etiology and pathogenesis of this form of valvular disease could not be determined with certainty. Clinical and pathological data indicate that the lesion in some cases may have an inflammatory basis, whereas in others it may represent the result of a noninflammatory degenerative process.

Certain features suggest that ischemia due to diminution of the vascular supply of the affected tissues may be the basic pathogenic factor productive of hyalinization and of other degenerative changes which subsequently proceed to calcification.

Further study of the blood supply of normal valves, and of the relationship of vascular lesions to this and to other forms of endocarditis, seems indicated.

REFERENCES

1. Aschoff, Ludwig: Lectures on Pathology, New York, 1924, P. B. Hoeber, Inc.
2. Cabot, R. C.: Facts on the Heart, Philadelphia, 1926, pp. 205-766, W. B. Saunders Co.
3. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: Valvular Diseases of the Heart, *Am. J. Path.*, 11: 193, 1926.
4. Haines, S. F., and Kepler, E. J.: Angina Pectoris Associated With Exophthalmic Goiter and Hyperfunctioning Adenomatous Goiter, *Med. Clin. N. Amer.*, 13: 1317, 1930.
5. Kerr, W. J., and Mettier, S. R.: The Circulation of the Heart Valves: Notes on the Embolic Basis for Endocarditis, *AM. HEART J.*, 1: 96, 1925.
6. Kerr, W. J., Mettier, S. R., and McCalla, R. L.: The Capillary Circulation of the Heart Valves in Relation to Rheumatic Fever, *Tr. A. Am. Physicians*, 43: 213, 1928.
7. Kugel, M. A.: Anatomical Studies on the Coronary Arteries and Their Branches. I. Arteria Anastomotica Auricularis Magna, *AM. HEART J.*, 3: 260, 1928.
8. Mönckeberg, J. G.: Der normale histologische Bau und die Sklerose der Aortenklappen, *Virchows Arch. f. path. Anat.*, 176: 472, 1904.
9. Ritter, S. A., Gross, Louis, and Kugel, M. A.: Blood Vessels in the Valves of Normal Human Hearts, From a Study of 700 Cases, *AM. HEART J.*, 3: 433, 1928.
10. Thalhimer, William: The Mechanism of the Development of Nonbacterial, Chronic Cardiovalvular Disease, *Arch. Int. Med.*, 30: 321, 1922.
11. Wells, H. G.: Chemical Pathology, Philadelphia, 1920, Ed. 4, W. B. Saunders Co.
12. Willius, F. A.: A Study of the Course of Rheumatic Heart Disease, *AM. HEART J.*, 3: 139, 1927.
13. Willius, F. A., and Giffin, H. Z.: The Anginal Syndrome in Pernicious Anemia, *Am. J. M. Sc.*, 174: 30, 1927.

PARTIAL BUNDLE-BRANCH BLOCK: A THEORETICAL
CONSIDERATION OF TRANSIENT NORMAL INTRA-
VENTRICULAR CONDUCTION IN THE PRESENCE
OF APPARENTLY COMPLETE BUNDLE-
BRANCH BLOCK*

GEORGE HERRMANN, M.D., NEW ORLEANS, LA., AND
RICHARD ASHMAN, PH.D., NASHVILLE, TENN.

BUNDLE-BRANCH block, complete or incomplete or defective intraventricular conduction, has long been considered an inalterable disturbance, the result of anatomical changes and therefore a reliable sign of very serious myocardial damage. Cases with from slight to complete conduction defects are of fairly frequent occurrence, while examples of partial or functional bundle-branch block are rare but nevertheless do occur in any medical clinic where a large number of patients with heart diseases are examined electrocardiographically.

In the majority of cases, the altered mechanism is considered to be permanent and complete. Partial or transient intraventricular conduction disturbances with which this paper deals, are relatively uncommon apparently because of the fact that in contrast to the situations in partial auriculoventricular block the intraventricularly blocked ventricle will promptly receive an impulse from the other ventricle under all but extraordinary circumstances.

Prognostically electrocardiographic findings indicating defective intraventricular conduction, especially if persistent, are significant of a grave myocardial damage. If the abnormalities are transitory, the prognosis is much better. This is to be especially emphasized when there is any consideration whatsoever of the subjection of a patient with such a disorder to any unusual diagnostic or therapeutic procedure such as intravenous injection or surgical operation. The latter procedure is likely, in itself or as a result of the anesthetic, to produce blood pressure changes or shock, or further adversely to affect the myocardium by depression.

In the presence of bundle-branch block the heart is laboring under the burden of an asynchronuous action of the two ventricles in addition to the effects of the widespread myocardial damage which locally has produced the defective intraventricular conduction. Apparently in such a heart in the presence of concomitant depression ahead and recovery behind, as the impulse spreads from the one ventricle to which it is conducted through the septum to the blocked-off ventricle, there

*From the Heart Station, Charity Hospital, and the Department of Medicine, Graduate and Undergraduate Schools of Medicine, Tulane University of Louisiana.

is likely to be established on relatively slight provocation with any even slight additional depression a circus rhythm which may result in fatal ventricular fibrillation.

The possible transient nature of these defects which have such a grave significance warrants emphasis. The consideration and the recognition of the fact that the block may be partial, though usually permanent, but that it is by no means always so, is important. The temporary or functional block is the result in a large measure of circulatory, nutritional or oxemic disturbances in the conduction system rather than of inalterable organic changes.

PREVIOUSLY REPORTED CASES

There have been reported about ten instances in which electrocardiographic evidences of changes in intraventricular conduction time have been recorded at different times of observation. After reviewing these cases we wish to record five more of this same type. Besides this we have had three most unusual cases in which we have been able to record sudden transitions from complete bundle-branch block to normal intraventricular conduction time for transient periods as the result of indirect vagus effects.

Lewis¹ as early as 1913, found a case in which transient block occurred in the right branch of the His bundle during a febrile attack. It was noted on the third day of the patient's illness when the fever ranged between 99° and 100.5°. It was absent on the fourth day and thereafter. Lewis' patient, a bookbinder, aged thirty-two years, had had dyspnea on walking for six years, an aching precordial pain for months, and a general "seedy" feeling which suggests the possibility of his having had a complicating acute endocarditis. The patient had an enlarged heart with free rheumatic aortic regurgitation. The electrocardiographic curves published with this case showed a shift in the origin of the T-waves which we might now consider very suggestive of coronary disease. Another subsequent curve interpreted as physiological is suggestive in the light of recent investigation of an incomplete bundle-branch block, which means some persistency of the defective intraventricular conduction. The QRS interval changed from 0.13 second to 0.10 second.

The same patient is commented upon by Carter² as Case 12 in his series. Carter's Case 20 was the first in which the electrocardiogram of the individual was obtained before as well as after the development of defective intraventricular conduction.

Cohn and Lewis,^{3,2} in a detailed microscopical study, found no recognizable pathological lesions in the complete serial sections of the conduction system of each of four cases. The discrepancy in these four instances between electrocardiographic and pathological findings

seems evidence sufficient, as the authors point out, that definite functional changes are not dependent absolutely upon recognizable anatomical changes. In one instance large blood spaces in and about the conduction system and pressure from these was considered to be a probable contributing factor in the precipitation of the bundle-branch block that had been recorded during the life of the patient.

Robinson,⁴ in further support of the functional nature of such changes in intraventricular conduction, reported another case in which the defective intraventricular conduction was clearly not based entirely on pathological lesions. He suggested that the disturbance was the result of "functional fatigue" and advanced the hypothesis that the interference was due to the accumulation of acid metabolites in the intraventricular conduction system. These chemical changes he felt, were the result of nutritional disturbances due to sclerosed coronary arteries and perhaps to other lesions of the myocardium.

Krumbhaar⁵ commented upon Lewis' unique case and presented one of his own, which was of further interest in that defective intraventricular conduction was observed in the process of development. His observations were of a man, seventy-six years old, with arteriosclerotic heart disease and mild anginoid attacks. His first examination showed marked left ventricular predominance with a QRS interval of about 0.10 second and an upright T-3, which signs we would today consider as evidence of incomplete bundle-branch block. One month later the electrocardiographic study showed complete bundle-branch block which persisted and was apparently permanently established.

Willius and Keith⁶ were fortunate enough to observe three cases in which there were conspicuous changes in the degree of the intraventricular conduction defects. All three of the cases were considered to be incomplete bundle-branch block. On the first observation in the first two, the QRS intervals and the characteristic T-wave changes strongly suggest that the bundle-branch block was practically complete. These authors emphasize the importance of recording these transient changes and explain them on the basis of myocardial fatigue, exaggerated by acute cardiac failure. The first case showed very little evidence of congestive failure. These cases again illustrate the fact that apparently profound disturbances in intraventricular conduction may be evanescent and the prognosis therefore would be more hopeful.

Von Kapff⁷ considered intracardiac hemorrhage as the most likely cause of the temporary intraventricular block in his case. Slight T-wave changes following the ectopic beats were considered evidence of a persistent slight conduction defect. Myocardial infarction must be considered a possible precipitating factor in this case as well as in some of the other cases.

Baker⁸ observed a case of transient bundle-branch block which disappeared with a slowing of the heart rate and failed to reappear with a rise in rate during exercise in which the administration of oxygen was carried out.

Leinbach and White⁹ reported a rare instance of transient two-to-one bundle-branch block, a phenomenon previously observed by Stenström, whose records, however, are published by these authors. The authors do not discuss the two instances of the unusual mechanism other than to comment upon the rarity of the condition.

Slater¹⁰ recently published a case of three-to-one and four-to-one partial bundle-branch block and discussed the theory of the subject at some length.*

COMMENTS

This review comprises the cases of transient bundle-branch block that appear in the literature up to the present time and to this series we will add our eight cases. It is to be noted that most of the previously reported cases usually presented defective conduction at one examination with later improvement, or less commonly, the reverse. The transitions were gradual, a result either of prolonged rest or of therapeutic measures or indiscretions. In a few instances the changes were abrupt from normal to abnormal intraventricular conduction, a result of progressive degenerative changes that suddenly became rapid as a result of infection or intracardiac circulatory disturbances, so that the defective intraventricular conduction or bundle-branch block was observed in the process of rapid development. In the one case reported, infection with fever may well have produced those essential temporary changes in the conduction tissues of the primary branches of the His bundle, which contributed to the transient block. In other cases changes in the vagus tone played a part. In some cases cardiac infarction as a result of coronary thrombosis has probably been the exciting cause. In most of the cases progressive myocardial exhaustion, anoxemia, functional fatigue, the accumulation of products of cell metabolism and congestive failure, were apparently precipitating factors.

This all supports the contention of Cohn and Lewis,³² proved by their careful anatomical studies, that the electrocardiographic findings are not necessarily dependent upon visible histological alterations. The branches of the His bundle, just as the main bundle itself, may be the seat of functional conduction disturbances even in the absence of microscopically recognizable pathological changes.

*After this was written an interesting paper by Wolff, Parkinson and White (*AM. HEART J.* 5: 685, 1930) has appeared in which they report eleven cases of bundle-branch block, mostly in otherwise healthy young people with paroxysms of tachycardia or auricular fibrillation. Abrupt transitions occurred spontaneously or as a result of exercise or atropinization from bundle-branch block with unusually short P-R intervals (0.1 sec.) to the normal physiological electrocardiogram with P-R intervals of normal duration. Such short P-R intervals during the periods of bundle-branch block are not characteristic of our own cases which probably depend upon a different mechanism.

THE PRESENT STUDY

The first three cases, those which we particularly wish to emphasize in this paper, are unusual in that seemingly profound intraventricular conduction disturbances with apparently complete bundle-branch block, were observed to change within one beat to complexes of an entirely different and absolutely normal contour, with normal short QRS intervals and vice versa. The importance of the observations lies in the fact that these records are strong evidence that the complete intraventricular conduction disturbances may be precipitated by changes in vagus tone and are thus in a large part functional in character. It seems highly improbable that anything but a nervous, chemical or acute mechanical pressure change could take place and give such results within the period of one heart cycle. Slight stretching or dilatation of the heart from increased intraventricular pressure shifts in an already disturbed intracardiac circulation, with perhaps the engorgement of the venous channels in and about the specialized conduction tissue, could all be theoretically held accountable for such sudden transitions in form of the ventricular complex. A narrow lesion which in itself does not obstruct the passage of impulses might conceivably be present in the conducting pathway and yet cause no delay of the impulse until one of the factors suggested precipitates block.

THREE INSTANCES OF SUDDEN INTRAVENTRICULAR CONDUCTION TRANSITIONS
CAUSED BY INDIRECT VAGUS EFFECTS IN PART AND BY ANOXEMIA
AND FATIGUE FOLLOWING EXERTION

The first three cases are all of sudden transition from complete bundle-branch block to normal intraventricular conduction which we observed in patients following the taking of a deep breath and the holding of it for from a few seconds to a minute with resulting indirect vagus effects. In one instance a slight amount of exertion was necessary before the intrathoracic and intracardiac pressure shifts were sufficient to produce the significant changes.

CASE 1.—A mother superior, aged fifty-five years, was referred to one of us for electrocardiographic and cardiac study by Dr. Joseph Larimore. This case has been briefly described in a series of unusual disturbances of the mechanism of the heart beat, reported by Dr. F. N. Wilson and one of us.¹¹ She had had a most unusual symptom complex. In January, 1920, she began to have weakness and indefinite abdominal distress. The spleen and the liver were found enlarged, as they had been six months previously. The white blood count revealed 27,000 leucocytes per cubic millimeter, 85 per cent of which were polymorphonuclear neutrophils. Very little history was elicited that was diagnostic of any of the usual syndromes, and no other abnormal findings were noted at that time.

The patient had had a "bilious attack" with slight icterus about fifteen years previously. She suffered no further illness until three years before admission when she had an attack of acute arthritis in the right knee. In the next year she began

to have attacks of severe pain in the chest, which seemed to have been of cardiac origin. The attacks recurred frequently during a period of three months and then spontaneously subsided.

In August, 1919, she suffered a heat stroke and had a recurrence of the acute attack of severe pain in the chest. Within a month an ulcer appeared on the right great toe and persisted for a month. Masses were found in the abdomen for the first time, and because of the presence of leucocytosis and a fever, along with the mass in the left flank, the patient was thought to have a perinephric abscess. An exploratory operation through the posterior route, however, revealed a normal kidney. Further exploration was then done through the abdominal wall anteriorly, and the spleen was found to be very large and completely infarcted. There was practically no normal splenic tissue left, and the organ was therefore removed. A left-sided pneumothorax developed after the operation, but otherwise postoperative convalescence was uneventful.

Gradual general clinical improvement continued until March, 1920, when there appeared an enlargement of the abdomen due to the accumulation of ascitic fluid. The intraabdominal tension became so great that the abdomen had to be tapped at intervals of two weeks. At each tapping two and one-half liters of straw colored fluid of low specific gravity were removed. The pleural cavities were found to contain similar fluid. After a third tapping, a diarrhea intervened, and this was apparently sufficient so to upset the water balance that the fluid temporarily stopped accumulating in the serous cavities.

In May, 1920, there was an acute left axillary adenitis associated with edema of the left arm. This cleared up spontaneously within a week. The patient had several attacks of acute gastro-enteritis at varying intervals. The leucocytosis persisted. The Wassermann reaction was negative, as was also the complement-fixation test for tuberculosis. Gradual improvement followed so that within a year the patient was able to reassume her heavy administrative duties and suffered only from constipation.

An intense pruritis over the entire body with slight edema of the ankles in the evening was occasionally troublesome. The liver edge remained about 6 or 8 centimeters below the costal margin. Urine contained a trace of albumin, and a few granular casts. The hyperleucocytosis of the blood persisted. A soft systolic murmur was heard in the mitral area; the lungs and pleura, however, were clear. The evidences of renal irritation entirely disappeared. The ascites recurred in disturbing amounts a year after she resumed her work. She was reported to Dr. Joseph Larimore to have died suddenly August 21, 1922, two and a half years after the first electrocardiographic examination.

COMMENTS ON ELECTROCARDIOGRAMS

During the taking of the electrocardiograms we noticed the long QRS interval and the diphasic T-waves, the evidences of complete bundle-branch block. The downwardly directed complexes of Lead III, although here definitely a part of the bundle-branch block caused us to try the effect of a respiratory test. This is routinely done by us in the presence of left ventricular predominance to determine the part played by the transverse position of the heart. The examination was made by asking the patient to take a deep breath and to hold it. While this was being done and the effects were on, the electrocardiograms were taken. During this maneuver we noticed that a sudden change in the form of the ventricular complex occurred. The slow,

broad QRS of the bundle-branch block was replaced by a sharp, quick deflection of normal contour and normal intraventricular conduction time. The maneuver was repeated several times, and the effects were photographed (Fig. 1). We noted that after a period of from a few seconds to a few minutes the bundle-branch block complexes invariably returned. A study of the curves showed that all the transitions took place suddenly as the rate, decreased by indirect vagus action,

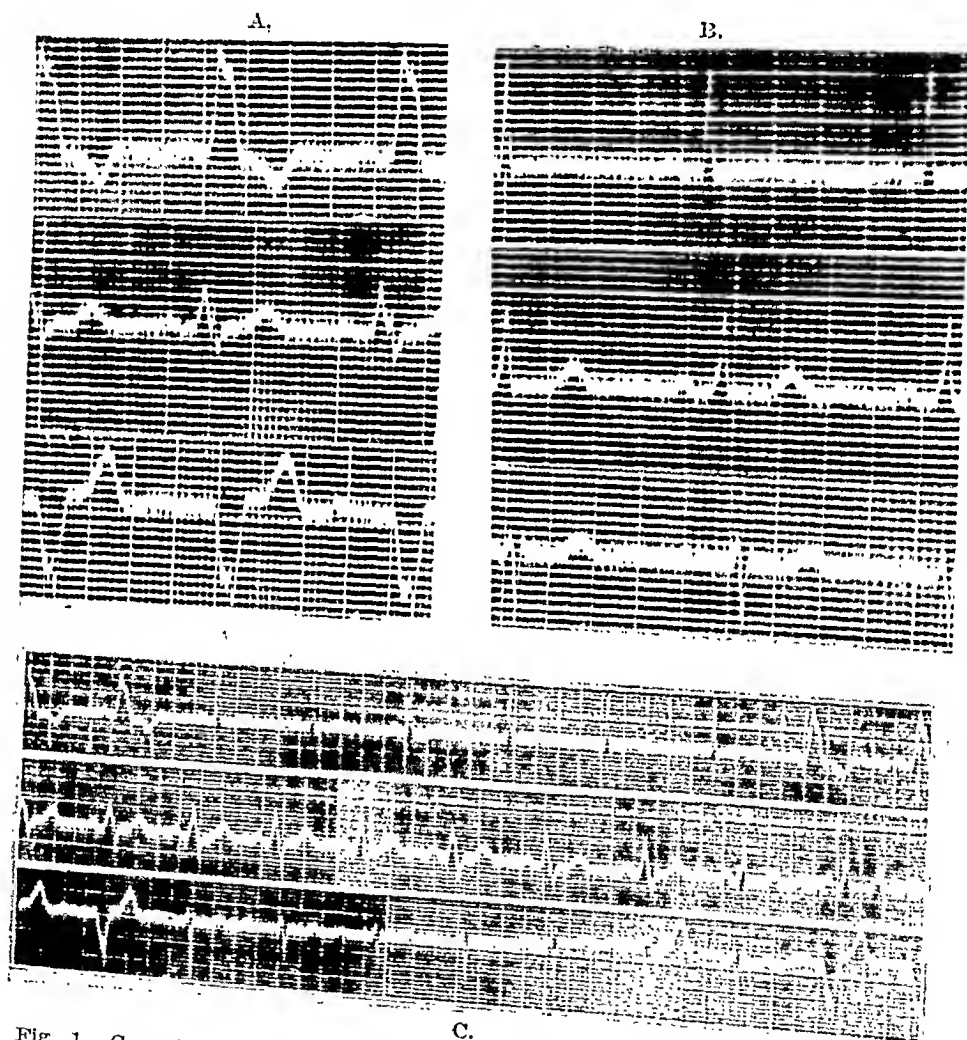


Fig. 1.—Case 1. A, Leads from above downward I, II, and III during complete bundle-branch block of the usual type (as all of our cases were). B, Leads I, II, and III during normal intraventricular conduction in the same patient after rest. C, Leads I, II, and III showing the abrupt transitions from complete bundle-branch block to absolutely normal conduction. See text.

dropped from about 75 to 65 per minute. Occasionally there was an alteration between the block and normal conduction suggesting a two-to-one partial block in the branch of the His bundle. This is shown in the last four complexes of Lead III (lower Fig. 1), although it might be argued that the first broad complex to appear after the normal intraventricular conduction period is a free wall ventricular escape. This, however, is quite unlikely.

The patient was then allowed to return home and to rest for a short period of time. When she was to be returned to the electrocardiographic laboratory, the attendants were instructed to bring her in a wheel chair to avoid the possible fatigue that the walking to the Heart Station may have incurred at the first examination. The curves taken after the rest without exertion showed normal intraventricular conduction. After mild exercise, consisting in lifting a five pound dumb-bell in each hand six or eight times with forward and sideward movements of the arms, the bundle-branch block complexes returned, and the respiratory test caused them to disappear temporarily again. Electrocardiograms recorded these facts, and examination of the curves corroborated the suspicion that there had been an extraordinary change from normal intraventricular conduction to a complete bundle-branch block (Fig. 1). There had been a change of the reverse character with exertion probably due to anoxemia of the conduction tissue and a release from the same again on resting.

CASE 2.—M. J., a negro woman, cook, aged 47 years, was admitted to Charity Hospital January 22, 1928, complaining of pain through the left chest and in to the back. She had had some dull pain in the abdomen and in the back for two years. During September, 1926, she began to notice some distress in the precordium, palpitation and shortness of breath on slight exertion. The distress became more and more marked and was brought about by less and less exertion. For some months there had been a distinct precordial distress with radiation to the back with the least effort. She had had some morning nausea but no vomiting. Swelling of the ankles and feet had been present for the past few months. Occasionally she suffered from a fainting spell. She became so incapacitated by September, 1928, that it was impossible for her to go up a flight of stairs.

Her father had died at the age of 57 years, her mother at 46 years of unknown causes. She had been married for 28 years but had had no children and no miscarriages. She had had no serious diseases in the past but was not sure whether or not she had had venereal diseases of any type. She chewed tobacco and snuff, used very little coffee and no alcoholic drinks.

Physical examination showed a huge, obese negro woman, 69 inches tall, weighing 190 pounds. She was uncomfortable even in the reclining position. The pupils reacted to light and in accommodation. The thyroid and the cervical lymph glands were very slightly enlarged. The neck veins, carotid and subclavian pulsations were slightly increased. The aorta was palpable in the suprasternal notch, and there was a distinct increase in the retromanubrial dullness. The cardiac outline extended 3 centimeters to the right and 14 centimeters to the left of the midsternal line. The apex impulse was just palpable in the fifth interspace in the midclavicular line, 13 centimeters to the left of the midsternal line. The aortic second sound was loudly accentuated and reverberating; the pulmonary second sound seemed to be reduplicated. A soft, systolic murmur was heard at the apex. The blood pressure was 212 mm. systolic and the diastolic sustained 140 mm. of mercury. The arteries were not distinctly abnormal. The lungs were clear and resonant throughout. There was a scar in the midline apparently from a previous gall bladder operation and drainage of the abdomen. Some tenderness was present over the liver. The hepatic border could not definitely be made out. The feet were slightly edematous.

The *laboratory examination* showed urine with 1.010 specific gravity, containing a trace of albumin, a few casts and epithelial cells. The blood chemistry studies revealed a nonprotein nitrogen level of 33 mg. per 100 c.c., a urea nitrogen of

16 mg., a creatinine of 1.2 mg., a uric acid of 3 mg. and a blood sugar of 100 mg. per 100 c.c. The Wassermann reaction was negative. The diagnoses were hypertensive heart disease; arteriosclerotic aortitis, possibly of luetic origin; coronary disease; anginal as well as congestive heart failure.

The *electrocardiograms* (Fig. 2) showed a complete bundle-branch block of the ordinary or common type. The QRS interval measured 0.18 second and the P-R interval 0.20 second. The complexes were broad, slurred, notched, and the T-waves were diphasic, thus completely fulfilling the bundle-branch block criteria. After three days' rest in bed, the electrocardiograms were found to be totally different from the preceding ones. The QRS complexes with an intraventricular conduction time of 0.08 second were recorded. Although normal in respect to the length of the QRS interval, the T-1 and T-2 waves were sharply negative, and there was some slurring in the R upstroke of Leads I and II, and the main deflection was deeply downward in Lead III.

The respiratory test at this time had little if any effect. Exercise, which consisted of a few squats, caused an immediate return of the bundle-branch block com-

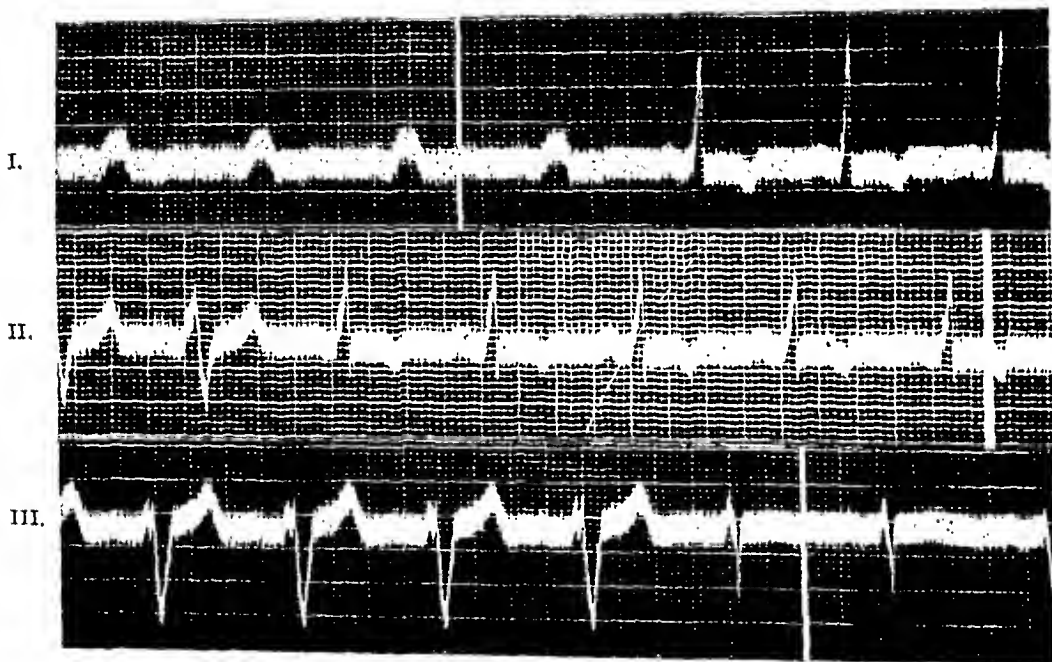


Fig. 2.—Case 2. Leads I, II and III with respiratory tests, vertical white signal lines marking beginning and end of deep inspiration. In all Leads reproduced, only the end is signalled.

plexes. After only slight exertion and by the application of the respiratory test complete transition from the bundle-branch QRS interval to the normal was recorded in all three leads, as the heart rate remained practically unchanged at 75 beats per minute.

The bundle-branch block was relieved by rest in bed, and it recurred with the slightest exertion. The patient was discharged, with directions to take theophylline ethylenediamine regularly, and digitalis when necessary under the direction of a physician. On March 15, 1930, she was still living and had about the same symptoms which she had had on admission. She was advised to return to the hospital for further study.

CASE 3.—Mrs. L. H., aged 37 years, a married, white housewife, came to Charity Hospital October 8, 1928, complaining of weakness. The trouble had begun several weeks before the patient entered the hospital and shortly after her marriage. She began feeling tired and was sometimes conscious that her heart beat too rapidly. Previous to this she had always been strong and able to do housework without

any difficulty. She had had measles and mumps as a child and influenza in 1918. One attack of sore throat occurred eight weeks before admission. It had been considered mild, but it was probably a serious streptococcal invasion. The patient had not menstruated for two months.

Physical Examination.—The patient was distinctly pale and weak but apparently not in pain. Her eyes were held closed, and her nose was pinched and her facies strained. The pupils were equal and reacted to light and in accommodation. The ears were normal and the teeth in good condition. The tongue was coated with a gray-white fur. The tonsils were largely submerged and showed signs of previous inflammation. There was, however, no evidence of an acute infection. Along the great vessels of the neck were conspicuous pulsations of a bounding, throbbing character synchronous with the heart beat. The chest was symmetrical, and expansion was fairly good and was equal on the two sides. No râles or suppression of breath sounds was noted. The apex impulse was not seen but could be felt over all the precordium. There were no thrills. A fairly loud, rough, blowing systolic murmur was heard best over the apex impulse and transmitted downward to the left and upward over the precordium to a less degree. The first sound was entirely replaced by a murmur. There was also a splitting of the first sound resembling closely a late diastolic murmur, rumbling in character. The systolic murmur was also heard at the aortic area, but later a high-pitched long diastolic aortic murmur became conspicuous. These murmurs could also be heard over the great vessels of the neck. Later a to-and-fro friction rub developed and persisted.

The abdomen was of normal contour and no masses were felt. On deep pressure in the left iliac fossa slight tenderness was found. The patient had a persistent fever. Electrocardiograms showed a complete bundle-branch block of the His bundle type. The blood count revealed a secondary anemia and a leucocytosis. The urine on October 8, 1928, showed many red cells and some pus cells, while a catheterized specimen on October 15, showed a trace of albumin, pus cells in masses and also occasional red blood cells. On October 23 there was only an occasional pus cell found, and on October 30 the urine was negative. There was a 40 per cent excretion of phthalein in two hours on October 22.

The vaginal examination revealed signs of an early pregnancy. The external os was plugged with secretion. The uterus was in a normal position and was freely moveable. The tubes were not enlarged, though they were slightly tender. The interruption of the pregnancy was considered but advised against because of the presence of an acute endocarditis probably of rheumatic origin and of the bundle-branch block. It was decided to tide her along and carefully observe her progress.

The blood pressure varied somewhat during the course of pregnancy, from 120/80 to 100/50. X-ray examination (October 26) showed the heart shadow normal with no evidence of dilatation of the aorta. The lung field appeared quite clear. The Wassermann test was negative on October 10. The feces examination on April 12, 1929, was negative for ova and parasites. A blood culture taken on October 23, 1928, showed a staphylococcus aureus in seventy-two hours with one colony per cubic centimeter of blood. A blood culture taken on November 28, 1928, showed no growth in seventy-two hours.

Progress.—The condition of the patient became worse during the first hospitalization. She began bleeding from the nose on October 24, 1928, and this condition recurred several times. On November 9, 1928, she complained of pain in the epigastrium and also in the left hypochondriac region. This pain was relieved by pressure. The symptoms of the acute endocardial infection subsided without definite signs of embolism, but the block persisted. She was an ardent Catholic opposed to abortion and very desirous of having a baby. Because of these facts and especially because of the persistence of the bundle-branch block she was allowed to continue in the pregnancy and to go home for a few months beginning January 6, 1929.

On returning to the hospital for the second time, March 10, the patient complained of palpitation and dizziness, particularly marked after exertion. The bundle-branch block, however, persisted as did also the signs of valvular heart disease, but no fever was present, nor were there any signs of acute endocardial infection. The electrocardiographic studies showed a persistence of the complete bundle-branch block in all curves taken before April 20. On this date a curve taken showed normal intraventricular conduction, but the bundle-branch block appeared again on April 30. She was observed daily up to the seventh and a half month of pregnancy when it was found after she had had good rest in bed that she actually had transient periods of normal conduction.

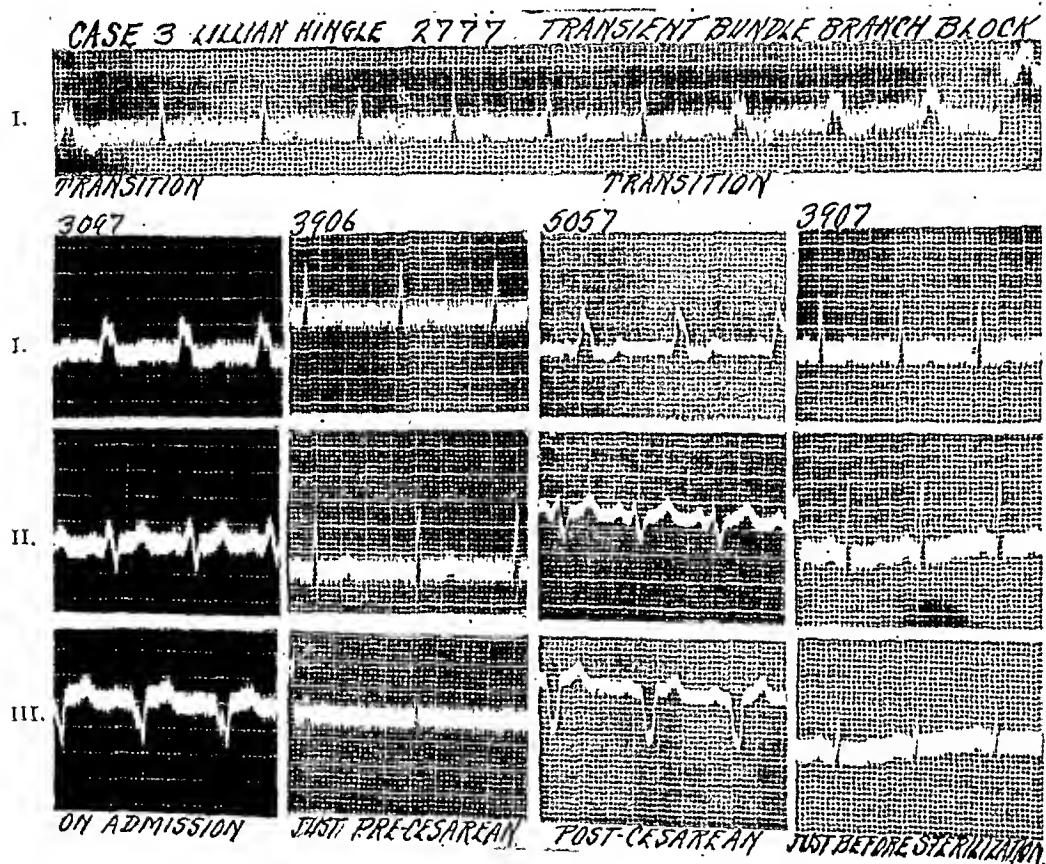


Fig. 3.—Case 3. Above, transition in Lead I. Below from left to right, the three Leads on admission, just before and just after the cesarean section, and just before sterilization.

Cesarean section was decided upon and was done during one of these periods of normal intraventricular conduction, on May 4, by Dr. E. L. King under local anesthesia and ethylene. A living baby was delivered. Bundle-branch block reappeared promptly postoperatively. Five days after Cesarean section, on May 9, normal conduction had returned, and the blood pressure was 106/48. The sterilization procedures which had been postponed were accomplished in a later period of normal intraventricular conduction. The patient was discharged from the hospital in fairly good condition.

The electrocardiograms (Fig. 3) show in the top strip the transition from bundle-branch block with a short, blunt, broad, slurred QRS complex measuring 0.14 second to a sharp narrow QRS of 0.06 interval for six beats and then another abrupt shift to the bundle-branch block. The P-R intervals are about 0.04 second longer during the period of conduction than they are during the block. The other

sets of curves, however, show greater differences in the intervals. Electrocardiogram #3097 shows intraventricular block with a rate of 100; #3906 conduction at 88; #5057 IV blocked at 91 and #3907 conduction at a rate of 90 per minute.

SOME OTHER INSTANCES OF CHANGES IN INTRAVENTRICULAR CONDUCTION

Besides the three special cases, in which by respiratory maneuvers it was possible to produce short periods of normal intraventricular conduction abruptly following a period of bundle-branch block, we have five other cases of high grades of partial bundle-branch block. In these, in the presence of partial or almost complete bundle-branch block or of defective intraventricular conduction with or without other mechanism or rhythm disturbances, there appeared at times normal short QRS intervals. Usually in the presence of an irregularity, after the longer rest periods and recovery from fatigue there occasionally appeared isolated or repeated complexes with intraventricular intervals of 0.08 second or less. These complexes almost invariably followed the longer pauses. Only two notable exceptions occurred in cases, not included in this series, with free aortic regurgitation in which the longer the pause the greater was the subsequent QRS interval and aberration. This paradoxical finding is possibly to be accounted for by the continuation of the regurgitant stream during diastole mechanically stretching the ventricular wall and interfering with the propagation of the impulse. The improved conduction is thus usually the result of the longer rest period of the fatigued tissue which allows more time for the removal of waste metabolic products as well as for the completion of anabolic processes which are probably slower in the conduction tissues which have an impaired circulation. This rate change is often, though not always, an important factor. One patient had several paroxysms of tachycardia in some of which there was normal conduction in others bundle block.

In these cases the prognosis seems to be better than in those in which the complete block has persisted, but not quite so good as in the cases in which periods of normal conduction can be secured, by rest or other means. The fact that the conduction system can occasionally yield normal appearing complexes after slightly longer rest periods indicates that fatigue plays an important part in the conduction disturbances and that rest with resulting improved intracardiac circulation, oxygenation, nutrition and elimination offers the possibility of restoration of normal function.

CASE 4.—G. A., a white laborer, aged 60 years, came into the hospital March 26, 1929, because of shortness of breath and rather rapid heart action. His symptoms had begun about four or five months previously when he first began to be troubled by attacks of rapid heart action during which he was conscious of every heart beat. The attacks appeared more frequently as time went on and were accompanied by severe "weak spells." A cough had been present for several months, and dyspnea had been noticed on exertion. About a month before admission he had become definitely orthopneic, and had been unable to lie in bed.

His feet and ankles showed some puffiness which gradually increased until easily recognizable edema was present, increasing until it was above the knees.

The family history was irrelevant, but in his past history he had had several infectious diseases which might have contributed to the heart disease. At about the age of fifteen years he had a severe attack of diphtheria which was not treated with antitoxin. He had had a mild typhoid infection. He denied venereal disease as a possible etiological factor. He had suffered a severe attack of influenza during the epidemic of 1918 and again in 1929. The latter seemingly precipitated his trouble.

The *physical examination* showed an extremely orthopneic white male, of sthenic habitus, measuring about 69 inches, and weighing about 180 pounds. Even in

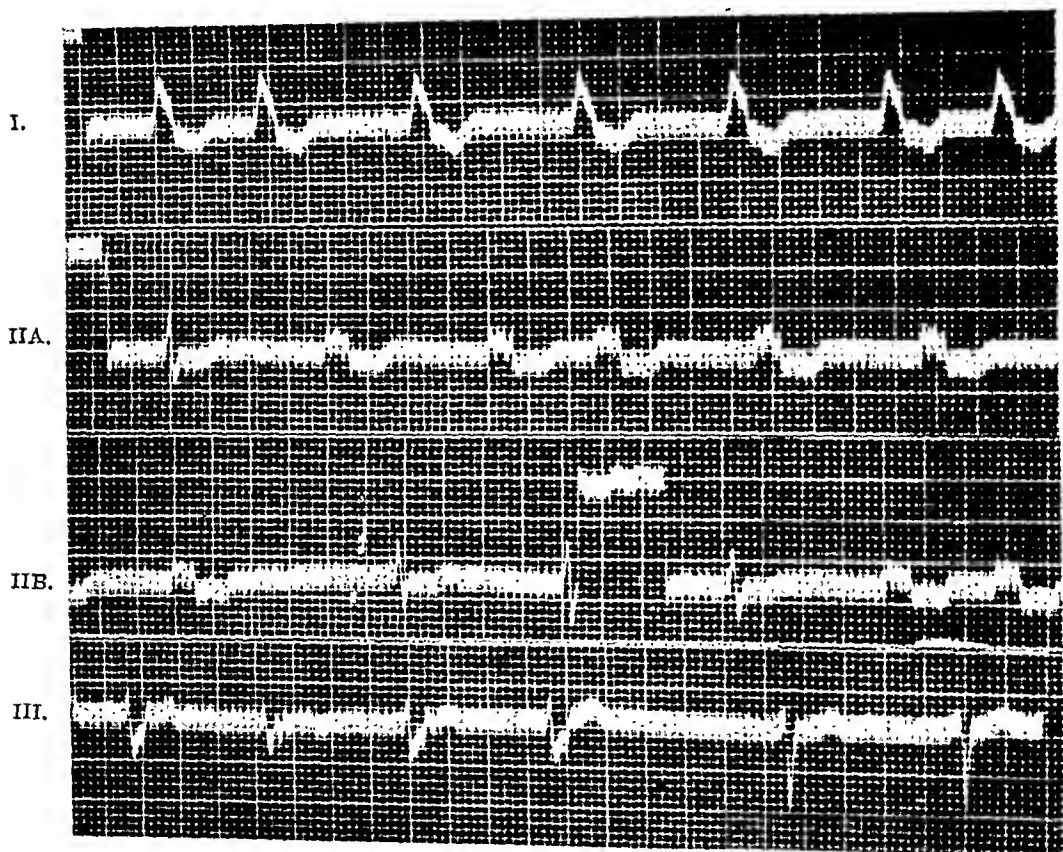


Fig. 4.—Case 4. Leads from above downward, I, II, III, showing broad and narrow QRS complexes of varying degrees of intraventricular conduction disturbance. At times the patient showed complete bundle-branch block with flutter; at other times there were normal conduction and flutter.

his propped-up position in bed he was distinctly dyspneic. The pupils reacted to light and in accommodation. The neck veins were engorged, and there was some systolic pulsation present in them. The maximum apex impulse was in the sixth interspace 14 centimeters from the midsternal line. Pulsations were regular and rapid. The retromanubrial dullness measured 5.5 centimeters. The cardiac outline extended 3 centimeters to the right and 14 centimeters to the left. A blowing, systolic murmur was heard in the mitral area. The pulse was full and bounding; at times it was 124 per minute and the rhythm was regular, at other times it was only 80 and definitely irregular, caused apparently by premature contractions. No pulse deficit was made out. The arteries were moderately sclerosed and large. The systolic blood pressure was 118 millimeters of mercury, and the diastolic was

92 mm. There were dullness at the lung bases posteriorly and crepitant râles throughout the basal area. Edema was present in the lower extremities and up about the knees.

The urine showed specific gravity of 1.010, albumin, no sugar and occasional hyalin casts. The P. S. P. excretion was 20 per cent in two hours. The Wassermann test was negative. The blood chemistry showed an NPN of 57 mg., creatinine 2, uric acid 5, and blood sugar 74 mg. per 100 c.c.

Electrocardiograms (Fig. 4) taken on admission, March 26, 1929, showed an auricular tachycardia of 134 per minute and a QRS interval of 0.06 second. The same disturbance was present on the following day and on April 6 there was a drop in rate to 120 to 100 and distinct evidence of defective intraventricular conduction, with a QRS interval of 0.12 second and a P-R and a suggestion of impure flutter rather than paroxysmal tachycardia. There were changes in T-waves, short paroxysms of rapid rhythm and an irregularity resembling two-to-one and three- or four-to-one block. Curves taken the next day showed an intraventricular conduction defect with regular rapid rhythm. The apparently complete bundle-branch block complexes were short, blunt and broad, simulating those of arborization block. The same condition was present on May 24, intraventricular block being of the ordinary type. On July 8 there was a return to the normal narrow ventricular complexes measuring 0.06 second with a presence of the auricular tachycardia persisting. The same conditions were found on July 11. On July 30 the electrocardiograms presented a bundle-branch block of the ordinary type with a QRS and a P-R interval of 0.16 second. Frequently ventricular and auricular ectopic beats were seen. In another day the complexes were distinctly blunt and shorter. Four days later these slight changes were still present. After treatment in the hospital for a month the electrocardiograms on August 30 showed perfectly normal ventricular complexes with a QRS interval of 0.06 and slightly defective auriculoventricular conduction time with an increase of P-R interval to 0.26 second and occasional blocking. The next day two-to-one block had developed, while the changes in the T-waves were more marked. Occasional ventricular ectopic beats or premature contractions appeared. The patient was discharged from the hospital considerably improved and remained in the Convalescent Home for a short time. On December 30 he was brought into the hospital *in extremis* with congestive failure and died the same day. The diagnosis had been arteriosclerotic and chronic nephritic heart disease with congestive failure apparently precipitated by influenza, attacks of paroxysmal tachycardia and bundle-branch block.

CASE 5.—M. J., a Syrian, aged 65 years, came into the Charity Hospital July 27, 1929, complaining of swelling of the feet and shortness of breath. Symptoms had been present since an attack of influenza four months previously. In this illness he had been confined to his bed for two months with chills and fever. He seemed to have been relieved somewhat by remaining in bed, but he still had palpitation and slight pain in the region of the heart. These troubled him especially after the eating of a heavy meal. Occasionally he was nauseated and vomited a greenish material. Nocturia disturbed each night's sleep four or five times. Swelling of the feet had been present for about three months, and had been quite severe at times when he attempted to get up and remain out of bed. He was totally incapacitated. He had taken only small amounts of digitalis as his only treatment. He had had no serious illness in the past. Two of his children were living, and four had died of unknown causes. His father had dropped dead, and his mother had probably died of heart disease for she had suffered from dyspnea and pain in the heart.

On physical examination the old man was found to be of sthenic habitus, 64 inches tall, and to weigh 122 pounds with very little panniculus. He was lying on his back apparently comfortable, exhibiting no dyspnea or cyanosis. The pupils reacted properly; all of his teeth were missing, no snags were present; the thyroid

and other neck glands were not abnormal; the neck veins and arteries presented no abnormal pulsation and nothing that was strikingly unusual; the apex impulse was not felt and could not be seen. No thrills or shocks were palpable. The cardiac retromanubrial dullness measured about 5.5 centimeters. The general cardiac dullness extended 2 centimeters to the right and 10 centimeters to the left of the midsternal line. The heart was slow and slightly irregular. The sounds, obscured by the conspicuous emphysema of the chest, were distant, and no definite murmurs could be made out. The arteries were slightly thickened; the blood pressure was 105 mm. Hg., systolic and 70 diastolic. Aside from emphysema the lungs presented nothing abnormal. The vital capacity was 2,000 cubic centimeters.

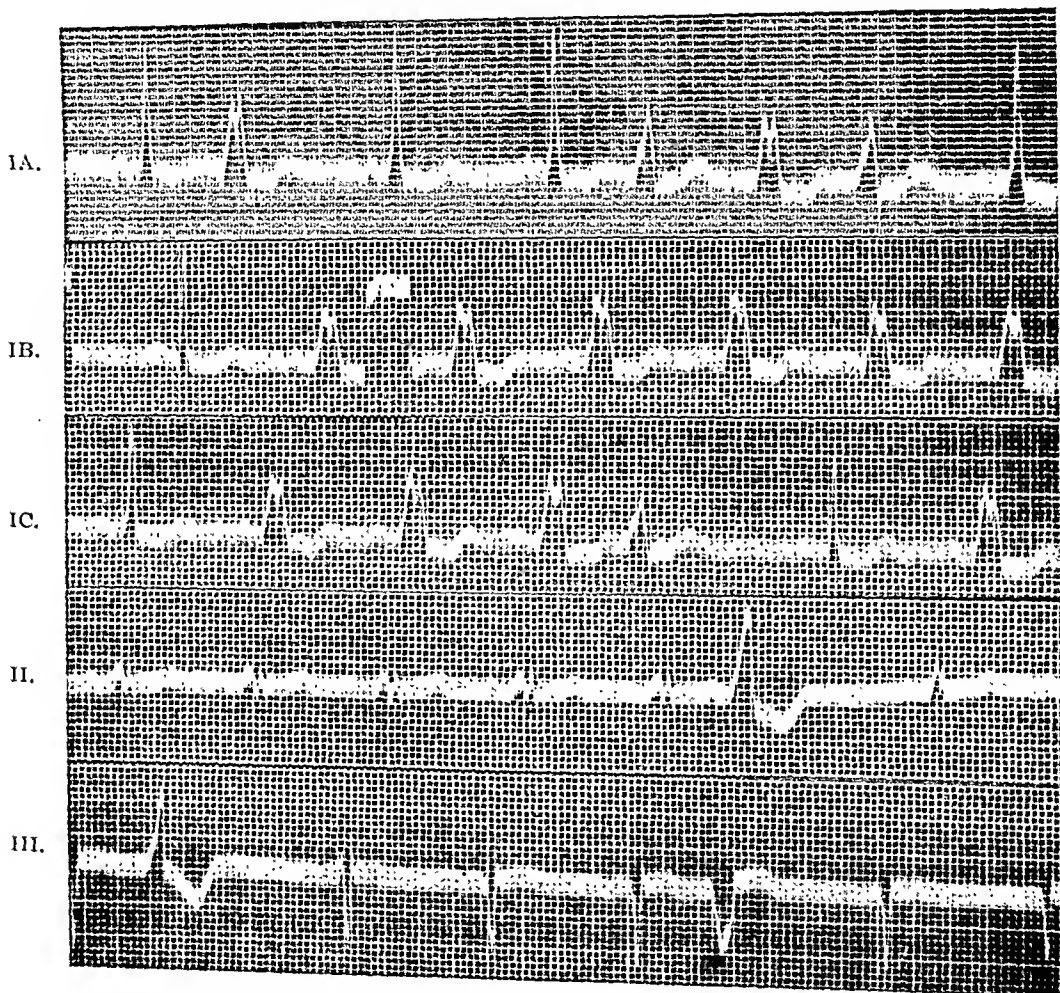


Fig. 5.—Case 5. From above downward, Leads I, I, I, II, III, (see text).

The abdomen was somewhat distended, no areas of tenderness were felt. The liver border was not felt, nor was the spleen abnormally large, and no ascites was present. The feet and legs showed a distinct edema. The urine was negative except for the presence of pus cells. The specific gravity was 1.010. The P.S.P. excretion was 30 per cent in two hours. The nonprotein nitrogen was 33.3 mg. per 100 cubic centimeters of blood; the urea nitrogen was 16.7 mg.; the creatinine 1.3 mg.; the uric acid 2 mg. and the blood sugar 93 mg. per 100 cubic centimeters of blood. The Wassermann test was not made.

Electrocardiograms (Fig. 5) taken on admission showed auricular fibrillation; QRS intervals of 0.08 second somewhat like Robinson's Case 5, with slightly slurred up-strokes of R-1 and downwardly directed main deflections in Lead III. Occa-

sional ectopic beats were present; here and there one was preceded by a clear cut P-wave suggesting a supraventricular origin with intraventricular block due to the persistence of fatigue as brought out by the prematurity. T-waves were negative to a great extent, and in Lead I and II there was a slight S-T segment shift from the iso-electric line. The electrocardiograms taken the next day showed the ventricular complexes preceded by P-waves to be predominating, and the more normal appearing complexes of a QRS of 0.07 second occurred only after long post-extrasystolic pauses. There predominated ventricular complexes of the ordinary bundle-branch block type, with the QRS measuring 0.16 second, a deep notching at the top and diphasically directed T-waves. Respiratory maneuvers apparently had little effect on the bundle-branch block. With complete rest in bed there was a return to normal appearing complexes. The patient was discharged distinctly improved and has been lost track of. He has not yet responded to the follow-up card.

CASE 6.—Mrs. E. P., housewife, white, aged 62 years, was admitted to Charity Hospital October 12, 1928 because of dizziness and pain in the heart, swelling of the abdomen and feet. The symptoms had been present for about three months and apparently had been precipitated by an acute respiratory infection. Cough had troubled her, with expectoration moderately free. She often vomited and felt nauseated after an attack of coughing. Her sleep has been disturbed as often as twelve times by nocturia with, however, the production of only small amounts of urine. Ankles and abdomen had become swollen shortly after the onset of the respiratory infection and cough. Palpitation and shortness of breath had been noted upon slight exertion and later even on eating and drinking. Dizziness and pain in the precordium region were noticed by the patient whenever she turned on her left side in bed. She had not been able to do any work for several weeks.

The *physical examination* revealed a white, French woman, 66 inches in height, weighing 160 pounds, of sthenic habitus, in a state of poor general nutrition, distinctly breathless even in a sitting position. Pterygia were present in both eyes; the pupils were contracted but reacted to light. There were many missing teeth and several infected snags remained.

The apex impulse was felt in the fifth interspace, 12.5 centimeters to the left of the midsternal line. The aortic arch was not palpable in the suprasternal notch; no abnormal pulsations were seen. The retromanubrial dullness measured 5.5 centimeters, and the area extended 3 centimeters to the right and 14 centimeters to the left of the midsternal line. The heart was rapid, 128 per minute. Numerous runs of rapid rhythm with premature beats were noted. The first sound at the apex was abrupt and prolonged; the second sound at the base, reduplicated. The pulse was small, soft, rapid, and there was a distinct deficit of about 36 beats between apex and radial. Blood pressure was systolic 130, and the diastolic was 94 millimeters of mercury. The peripheral arteries were not definitely sclerosed. Definite râles were found at both lung bases posteriorly. The lungs were somewhat distended and emphysematous.

The abdomen was greatly distended by a marked ascites. A distinctly sharp edge of an enlarged liver was found. There was slight edema of the extremities.

Urine showed 1.020 specific gravity, contained 3 per cent albumin, no sugar and no casts, and only a few pus cells. The Wassermann reaction was negative.

Electrocardiograms (Fig. 6) taken on October 12 showed a high grade of auricular fibrillation, short, blunt, broad complexes with defective intraventricular conduction. The QRS intervals measuring about 0.12 to 0.14 second. Occasional premature contractions with a QRS of 0.8 second were seen. The curves of the following day were quite similar. After three days' rest in bed the complexes were not so blunt, and the QRS intervals measured 0.06 to 0.08 second, the rhythm was

quite regular except for occasional ectopic beats. No definite P-waves were seen. On March 16, 1929, there was a return to the broad complexes in some parts of the curves taken. The QRS intervals increased from 0.08 second to 0.14 second. The interval length for the most part varied irregularly with occasional ectopic beats and occasional short paroxysms of regular rhythm which was apparently of nodal or junctional origin. On March 17 the rate was very much reduced, no paroxysms were photographed, and on March 19 conditions were about the same. On December 6 there was little change except that the complexes were getting

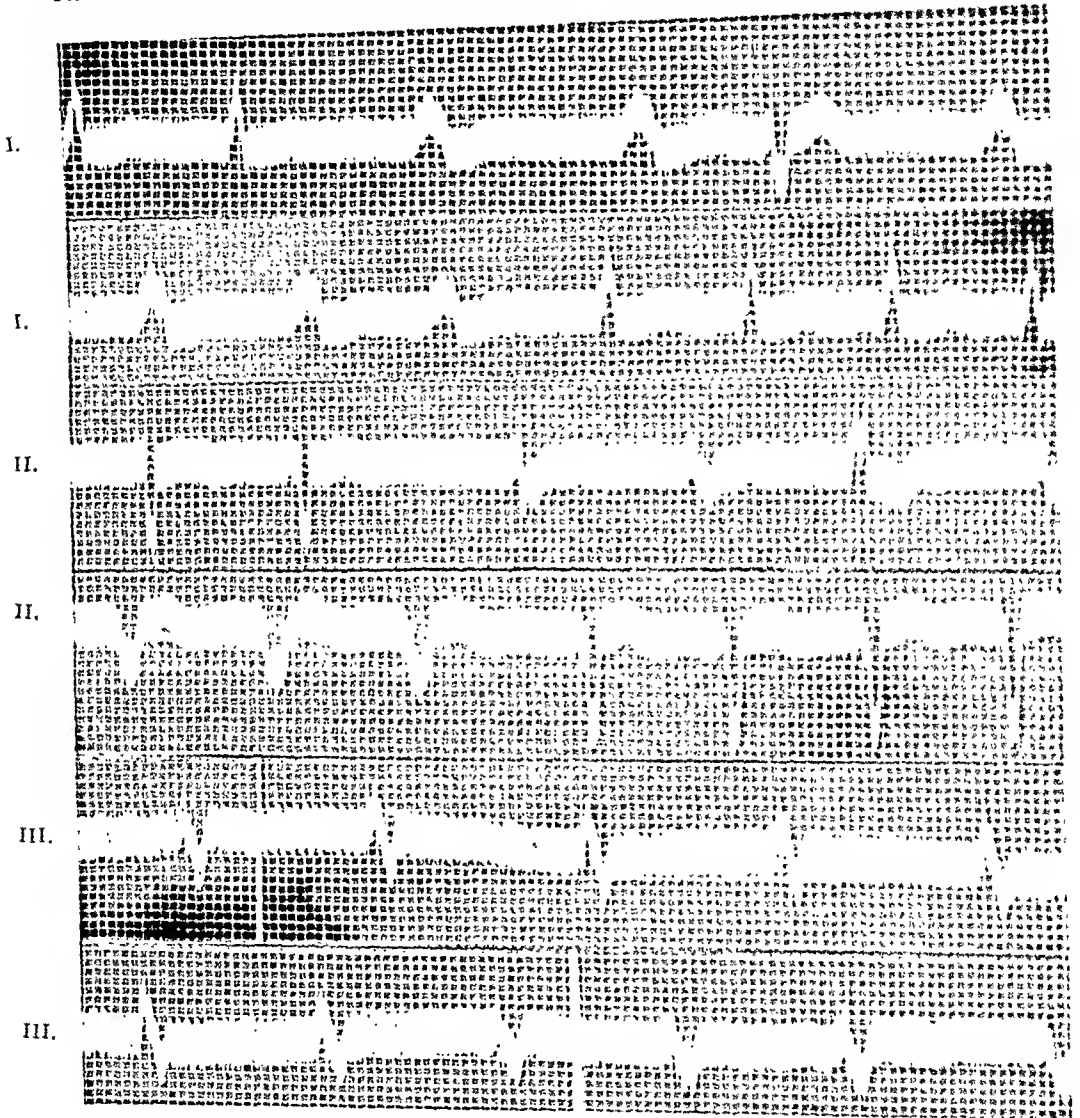


Fig. 6.—Case 6. Leads from above downward, I, I, II, II, III, III. Deep inspiration signalled.

shorter and more blunt. This was especially marked in the very low, broad, blunt complexes of March 5, 6, 7. Bizarre complexes were frequently seen among the many premature contractions. The patient failed to improve much but was discharged and died about one week after her return home.

CASE 7.—P. S., a white decorator, aged 66 years, entered the hospital on April 11, 1930, because of shortness of breath and palpitation. The onset of these symptoms dated back to two and a half years before his entrance into the hospital. Swelling of the ankles and abdomen began about this same time. All symptoms disappeared during the night and were banished for several weeks after a period

of rest in bed even without medication. One year after the onset, treatment with digitalis was started and continued irregularly from that time for the next year and a half. Frequent periods of rest in bed were necessary.

The family history revealed the facts that the patient's mother had died at 63 years of "heart trouble" and his father of "dropsy" at the age of 53 years. The patient had had mumps as a child and pneumonia at the age of twelve. Gonorrhea contracted at the age of 25 completed the list of past diseases. He was married at 21 years and was the father of 12 children of whom there were 7 living and well. There had been no miscarriages.

The *physical examination* showed an hypersthenic individual weighing about 150 pounds and measuring about 64 inches. The pupils reacted to light and in accommodation. The tonsils were small and red. His teeth showed pyorrhea and some caries. The aortic arch was barely palpable in the suprasternal notch, but there was evidence of dilatation of the aorta. The apex beat was in the fifth interspace outside the left midclavicular line. The heart rate was 50 and the

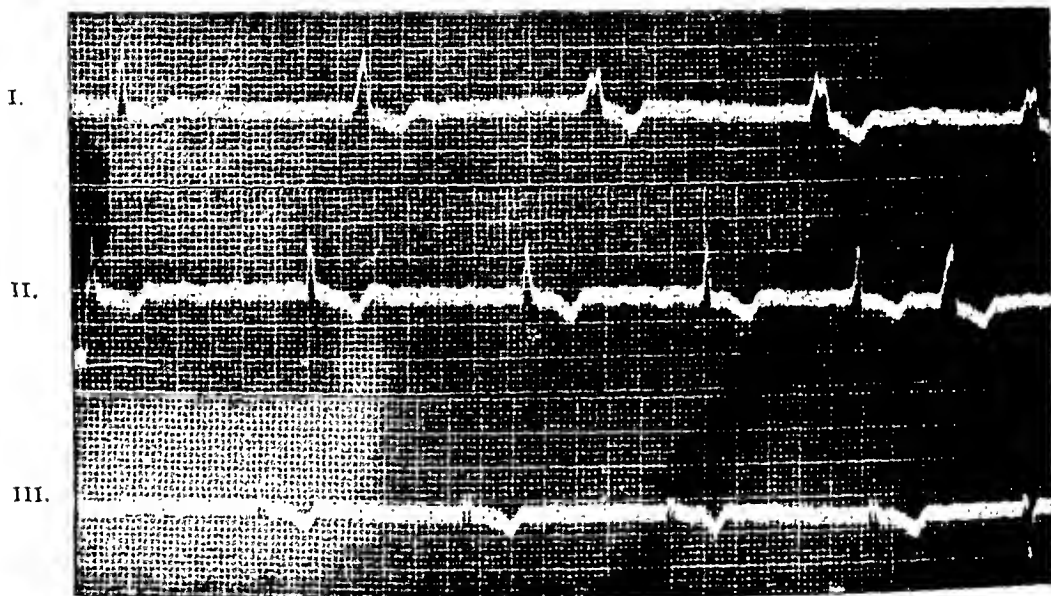


Fig. 7.—Case 7. Auricular fibrillation with changing intraventricular conduction time especially in Lead I.

rhythm irregular with many premature contractions. There was a soft right basal systolic and a very soft apical systolic murmur just within the nipple line. The arteries showed moderate arteriosclerosis. The blood pressure was systolic 120 millimeters of mercury and diastolic 90. There were moist râles at the bases of the lungs. The abdomen was full and soft.

The urine showed a specific gravity of 1.013 and was negative except for the presence of many hyaline and granular casts. The P. S. P. excretion was 45 per cent. The Wassermann test was negative. The blood chemistry showed nonprotein nitrogen 44.4; urea nitrogen 23; creatinine 1.42; uric acid 4.44; and blood sugar 108 mg. per 100 cubic centimeters. The hemoglobin was 80 per cent, the red blood cells numbered 3,281,000 and the white blood cells 4,000 per cubic millimeter. The differential count showed: small mononuclears 26; large mononuclears 6; and neutrophilic polymorphonuclear cells 68.

The first electrocardiogram (Fig. 7) taken April 16 showed auricular fibrillation, left ventricular predominance, questionable defective intraventricular conduction with a QRS of from 0.06 to 0.08 second. The heart rate was slow, 56 beats per

minute. There were occasional ventricular premature contractions as presented in complex 4 of Lead I. After complex 5 (Lead I) there is a probable shift to an idioventricular pacemaker with an increase of the QRS to 0.12 and 0.14 sec. in the last four complexes. In Lead III after a narrow 0.08 second QRS complex with upright T-waves there are four blunt, broad 0.10 second QRS complexes with negative T-waves. On April 17 there was less conspicuous transient defective intraventricular conduction along with auricular fibrillation with the rate increased about 10 beats per minute. The QRS was 0.08 to 0.10, and the rate was 60. On April 21 the rate was 74 with auricular fibrillation and more frequent ventricular ectopic beats or aberration, and the QRS, 0.09. T-1, T-2 and T-3 were negative. On April 22 the rate was 78 and the QRS 0.09 to 0.12 and sometimes

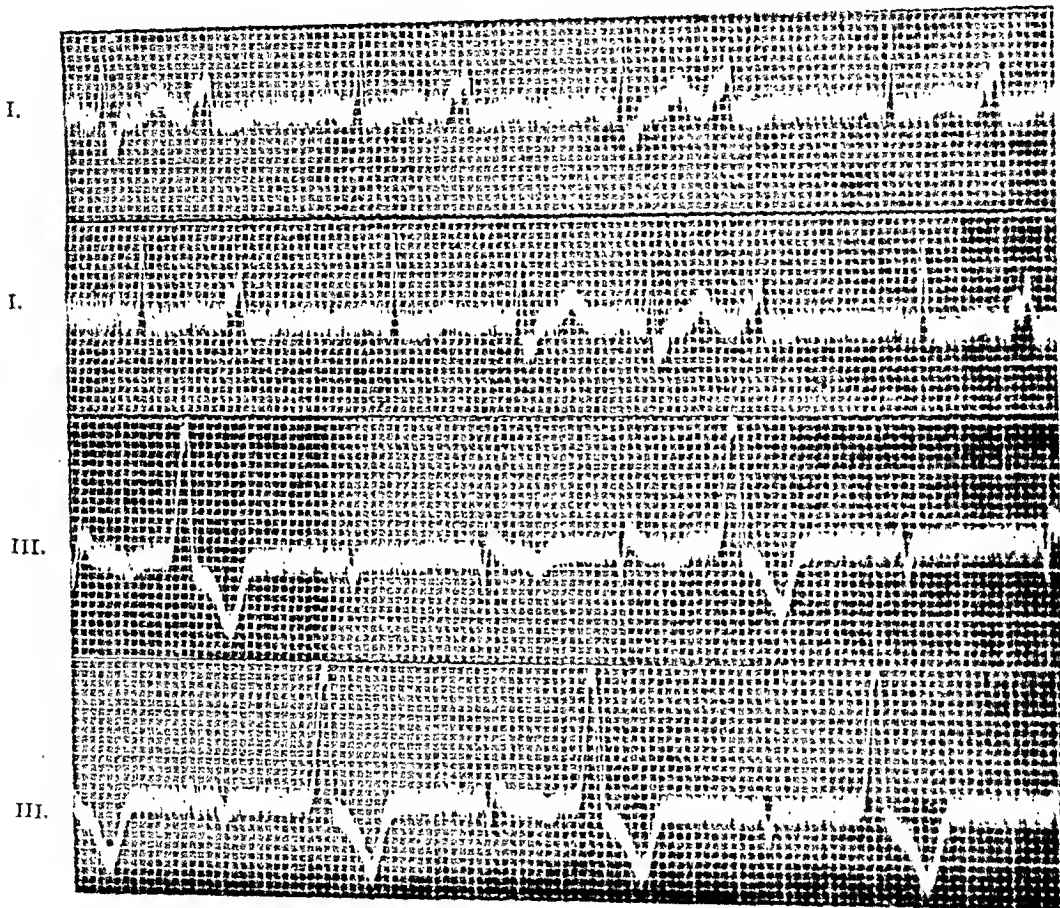


Fig. 8.—Case 8. Leads, from above downward, I, I, III, III. Note abrupt changes in QRS width in complexes following compensatory pauses.

broader complexes and greater aberration after longer rests. On April 26 the rate was 88 and the QRS 0.08 and there were rarely broad complexes with aberration. Auricular fibrillation persisted, and on June 14 with a rate of 110 to 120 the QRS measured never more than 0.08 second. Left ventricular predominance with a rise of the S-wave on deep inspiration and negative T-1, T-2 and positive T-3 were present, but no broad and bizarre complexes appeared.

He was given digitalis again along with theophylline ethylenediamine and a low-protein, salt-poor diet on which he improved considerably. After the patient was discharged from the hospital on April 22 edema recurred, and he returned to the out-patient clinic where he responded to the digitalis, squills and mercury pill, and normal sinus mechanism was established. He was in regular follow-up attendance until December 15, 1930, when he died suddenly.

CASE 8.—Mrs. M. A., a white housewife, aged 57 years, came into the Heart Station of Charity Hospital June 10, complaining of shortness of breath, palpitation, dizziness, pain in the left arm and swelling of the feet and ankles. The symptoms had come on insidiously, and dyspnea had become noticeable two years before admission. The vertigo was troublesome for three months and the pain for six weeks, previous to the time she presented herself for treatment. Paroxysms of dyspnea and palpitation were noted even at rest at times, but always on exertion. The pain in the left arm was precipitated by effort and excitement and extended from the shoulder to the elbow. It had been sharp at times but was for the most part dull and of short duration. She had never had an attack of syncope but had felt weak and faint at times.

The *physical examination* revealed an obese middle-aged woman of sthenic habitus moderately orthopneic at times and with a slight tinge of cyanosis. The teeth had all been removed. The thyroid isthmus was slightly enlarged. The heart apex impulse was felt in the fifth interspace 10 centimeters to the left of the midsternal line; the aortic arch was not palpable in the suprasternal notch. The cardiac dullness extended 3 centimeters to the right and 12 centimeters to the left of the midsternal line. The teleroentgenogram showed an arch of 4.6 centimeters with a transverse and longitudinal diameter of 16 centimeters each. The heart rhythm was irregular with premature contractions appearing regularly after every other or every fourth beat at times. The aortic second sound was accentuated. No significant murmurs were heard. The blood pressure was 162 mg. Hg. systolic and 88 diastolic. The peripheral arteries were not appreciably abnormal for the patient's age. The lungs were negative. There were only a slight tenderness in the liver region and a questionable edema of the ankles.

The urine was of 1.010 specific gravity and contained no albumin or sugar or casts but a few pus cells. The nonprotein nitrogen was 33.3 mg. and the blood sugar 78 mg. per 100 c.c. of blood. The blood Wassermann test was negative.

The *electrocardiograms* (Fig. 8) showed frequent ventricular premature contractions producing a bigeminy most of the time. A closer study of the narrower supraventricular complexes revealed distinct changes in the QRS width and especially the breadth of the S-waves. After the longer postextrasystolic pauses the QRS interval measured about 0.07 second, while after the shorter pauses the QRS interval increased to 0.10 second and when the rate was increased, abolishing the ectopic beats and compensatory pauses, the QRS interval broadened to 0.12 second. In Lead II this state of affairs was present throughout. In Lead III the changes were less readily observed but were nevertheless clearly present. The findings suggested a degree of partial, perhaps incomplete, bundle-branch block in which the conduction was at a critical level such that slight changes in rate and the length of the rest period were sufficient to cause sudden and pronounced changes in the intraventricular conduction time. This change was sudden, of an all-or-none character, and the partial intraventricular disturbance, even though slight, was of Type II of partial intraventricular block.

THEORETICAL DISCUSSION

A consideration of certain physiological matters is essential adequately to present our point of view concerning the mechanism of partial bundle-branch block as the intraventricular counterpart of partial A-V block. It will be necessary for the sake of orientation to discuss in detail the theory of A-V block.

Much evidence has accumulated which indicates unmistakably that the fundamental phenomena of conduction are everywhere the same,

in nerve, in skeletal muscle, and in cardiac muscle, whether the latter be a part of the auriculo-ventricular junction, the auricular muscle, the ventricular muscle, or the Purkinje fibers. This view is now widely accepted, although there are those who still cling to an opposing conception, at least so far as the A-V junction is concerned (Mobitz,¹² 1924, 1928; Straub and Kleemann,²⁶ 1917). The clinical cases herein reported afford an opportunity of discussing certain matters which have up to the present not received adequate attention, or emphasis and which are still not generally understood.

Auriculo-Ventricular Block

Wenckebach has recognized and described two main kinds of A-V block, named by Mobitz^{12b} Type I and Type II. Each, of course, may appear in variously modified form. But, for clarity in discussion, we shall briefly characterize the essential features of each. The first type is the one ordinarily regarded as typical of heart-block, showing as it does the occasional or more frequent dropped ventricular beats; the comparatively rapid, often apparently normal, conduction of the following auricular impulse; and the more or less gradual prolongation of subsequent P-R intervals until an impulse fails to reach the ventricle and another beat is dropped producing "Wenckebach's periods." In the severer stages of this type, we observe 2:1 or more rarely the higher grades of block or complete block.

This type of block is now comparatively well understood. An explanation similar to that offered by us has been adapted to the various sub-types of block in an interesting paper by Scherf.¹⁵ Wenckebach and Winterberg's¹⁴ conception of the mechanism of Type I block is much the same. Beginning with the dropped beat, the explanation previously advanced by us is this. The auricular impulse that is to be blocked penetrates the junction to a given depth and is blocked at a transverse plane, *B*. Because it is blocked, the tissue distal to plane *B*, not having responded, has extra time for recovery. The next impulse from the sinus consequently finds the region *C*, immediately beyond *B*, responsive and is, therefore, transmitted to the ventricle. The third impulse finds *C* depressed because of its previous response, and is transmitted more slowly. The fourth impulse finds *C* still more depressed, either because of cumulative fatigue or for some other reason, and consequently either fails to cause a response of *C*, or is transmitted still more slowly. Sooner or later unless the factors leading to recovery of *C* balance those responsible for its depression, another impulse must fail to reach the ventricle. In the most stable form of partial block, 2:1, *C* is capable of responding only to every other impulse.

The less common and less understood variety of A-V block is Type II. It would be premature to attempt to explain it, but we may examine its outstanding characteristics. First observed by Wenckebach¹⁵ and by Hay¹⁶ Type II block shows no change in the length of

the A-V interval at the time of transition from one stage of block to another. The A-V intervals remain constant throughout, and, in perhaps the majority of cases, within normal limits. Although protean in its manifestations, it is in cases of block of Type II that we commonly see abrupt transitions from apparently normal conduction to temporary complete block or the reverse; or two or more successive transmissions of the auricular impulse to the ventricle followed by two or more successive failures, these occurring in irregular sequence. A good example of the latter is illustrated by Mobitz.¹² Abrupt transition from an apparently normal mechanism to complete block is well shown in Case 4 of Wilson and Herrmann²¹ and by Ashman and Herrmann.¹⁷ This is the form of block which finds its counterpart in intraventricular conduction in the cases herein discussed, where there is abrupt transition from seemingly complete bundle-branch block to normal intraventricular conduction or the reverse. Whether or not the latter block was actually complete is, perhaps, questionable, as will be mentioned below.

Scherf¹³ has made the interesting suggestion that in A-V block of Type II, when the conduction time for impulses passing to the ventricles is within normal limits, the damaged or depressed area in the conducting pathway is practically limited to a plane cutting transversely across the A-V node or bundle. Thus, when the impulse does cross the extremely narrow gap, the loss of time is negligible. This explanation is in complete harmony with the converse conception which Herrmann and Ashman¹⁸ had expressed to account for the phenomenally long conduction times, ranging up to 1.01 second in one of their cases, namely, that a very long A-V interval is the result of a great breadth of injured or depressed tissue through which the impulse must make its way. They also stated that a shorter conduction time, other things being equal, argued for a shorter stretch of depressed tissue in the conducting pathway.

Intraventricular Block

We are now in a position to inquire whether, in intraventricular block, we may recognize the counterparts of Type I and of Type II A-V block. One of the chief problems which confronts us is to explain why a sequence of events similar to those observed in partial A-V block of Type I with "dropped beats," has never been observed in the human case. We cannot look for the answer in a fundamental difference between the physiological properties of the bundle or bundle-branch tissue, and the A-V junction as Mobitz^{12a} believed, but rather in the differences in the anatomical relationships and conditions. Substantiation of this view is found in experiments of Scherf and Shookhoff.¹⁹ After cutting the left bundle-branch and temporarily compressing the right, regular Wenckebach periods, i.e., typical 3:2, 4:3 grades of heart-block, were recorded. In discussing the rea-

sons for the rarity of partial bundle-branch block, and the absence of reports of bundle-branch block of the 4:3, or 3:2 type, we must briefly consider the various possibilities. As a first stage in block, there may be slight or moderate delay in one bundle-branch, a delay of from 0.005 to about 0.04 second. Such delay results in the well-known electrocardiographic picture of incomplete bundle-branch block. In the next stage the prolongation of intraventricular conduction time may be greater. Here the impulse, sweeping normally through the opposite ventricle, penetrates the septum and activates the ventricle whose bundle-branch is damaged before that ventricle can be reached by the impulse delayed in its own branch. When, and if, this latter impulse does reach its ventricle, the tissue is refractory. The electrocardiographic picture is that of complete bundle-branch block. To quote a recent paper by Slater¹⁰ "innumerable cases which are called complete bundle-branch block are in reality incomplete bundle-branch block." And further, according to Slater, "there is a matter of only 0.035 to 0.05 second for the play of the various types of incomplete bundle-branch block to make itself manifest." "This latter fact," he says, "is what has made it so hard to find clinical examples of the various types of block to correspond to those of the A-V block."

Let us apply this conception to a hypothetical 4:3 bundle-branch block, of Type I which, but for the reason Slater gives, would resemble typical 4:3 A-V block. The first impulse will pass the defective bundle-branch with little or no delay. Thus, the ventricular complex is of practically normal form. The next impulse, however, to judge from analogy with A-V conduction, is considerably delayed. The corresponding complex is, therefore, typical of those of complete bundle-branch block. And the same thing will be true of the next two complexes, in which the delay is even greater. The fifth impulse, however, goes through, and again we should expect to see a complex of relatively normal configuration. The result will be an electrocardiogram in which every fourth QRS is relatively narrow, the others broad. This is precisely the type of electrocardiogram Slater publishes. His figure may, therefore, represent 4:3, 3:2 partial block of Type I. On the other hand, great progressive prolongation of the P-R intervals in partial heart-block with dropped beats is not always seen. And experimentally all degrees of prolongation of conduction time are seen in compression block, from those in which block occurs with hardly measurable variations in the intervals to those in which the prolongation and variation is extreme (Ashman, unpublished observations). Therefore, unless there be some explanation other than that of Slater, it is hard to understand why the type of block under discussion is not sometimes observed.

But let us carry our analysis still further. After 4:3 and 3:2 partial A-V block of Type I, we find 2:1 block, which as Wenekebach and Winterberg¹⁴ point out cannot be identified as to type, unless it is known

that the same heart at other times presents the typical picture of one or the other type of intraventricular block. Leinbach and White⁹ have reported a very clear example of 2:1 partial bundle-branch block and one from Stenström,²⁷ and other illustrations are to be found in Wenckebach and Winterberg.¹⁴ It is impossible, of course, to say whether they are of Type I or Type II.

It is generally stated, and there is no reason to question the statement, that 3:1 block is the stage following 2:1 A-V block of Type I. That it is rarely seen is a consequence of idioventricular activity. The ventricle rarely waits for the third impulse to come through, but escapes and thus the electrocardiographic picture of complete heart-block is seen. In the bundle branch, however, if the arguments of Slater tell the whole story, there is no apparent reason why partial 2:1, 3:1, 4:1 or even higher grades of block should not be seen relatively frequently. The electrocardiogram, of course, should show more or less frequent, relatively normal, ventricular complexes, each pair separated by one, two or more complete bundle-branch block complexes. It is manifestly impossible to prove that Slater's case does not represent just such a mechanism, i.e., 3:1, 4:1 block of Type I.

At the same time, however, a third possibility exists. Slater's electrocardiograms may, as he himself believes, portray a 3:1, 4:1 block of Type II. But it is quite impossible to decide with certainty between these three explanations.

It should now be evident from our discussion that the arguments advanced by Slater do not satisfactorily explain why partial bundle-branch block, demonstrably of either type, is such a rarity. The physiologically satisfactory answer is given by Wilson and Herrmann.²⁰ In contrast to the situation in partial A-V block, the region of local depression in bundle-branch block is reached from both sides by the impulse, first through the branch from above and a little later from below by the impulse from the opposite ventricle. The consequence is that every impulse finds the physiological state of the depressed region the same. Excepting under unusual circumstances, therefore, there is no possibility of variation in the behavior of that region, or, in other words, of the appearance of partial block. Partial block of Type I can only appear, as we have pointed out, when some part of the conducting pathway periodically fails to respond and, therefore, gains additional time for rest and recovery. Appreciation of this point of view will enable one to see that the other arguments to explain the rarity of partial bundle-branch block are superfluous.

However, physiological states and structural relationships of depressed and nondepressed segments of the bundle branch can be imagined which could lead to the appearance of partial block of Type I. For example, a condition of irreciprocal conduction or unidirectional block may be present. Ashman and Hafkesbring, using ven-

tricular strips from the turtle heart, demonstrated that an impulse may pass a depressed region, if it travels first through normal, then enters strongly depressed, then slightly depressed and then reenters normal muscle. But if the impulse was required to travel in the opposite direction, it was blocked. Of course, the degree of depression must be neither too small nor too great. According to their interpretation, the blocked impulse failed to pass because it failed to cause a response of the more strongly depressed region. Thus a proper orientation of less and more depressed areas in a bundle-branch block would make possible the appearance of Type I partial block by protecting the region of greater depression from the effect of the impulse from the other ventricle. It is this latter effect which, as Wilson and Herrmann²¹ believe, ordinarily prevents the appearance of partial bundle-branch block.

In this connection it is interesting that in accounting for a human case of irreciprocal conduction in which, in the presence of complete A-V block, there was V-A conduction, Wolferth²² was independently forced to assume that the same orientation of more and less depressed muscle was present which Ashman and Hafkesbring found by experiment did produce the condition. Other anatomical arrangements of the depressed regions in a bundle-branch might make possible the appearance of the 4:3 type of block, as, for example, in Scherf and Shookhoff's¹⁹ experiments, but, with the latter exception, the phenomenon would apparently depend upon unidirectional block. The 2:1 bundle-branch block observed by Leinbach and White and the 4:1, 3:1 block in Slater's case may very possibly have been Type I intraventricular block and be explained on this basis.

COMMENTS RELATIVE TO ADAPTABILITY OF THEORETICAL CONSIDERATION TO CLINICAL CASES

As an important consequence of our analyses, there emerges the fact that it is impossible to recognize the type of intraventricular block excepting in rare cases. In all supposed instances one must be sure that the heart rhythm is regular. One example is hypothetical since it has not been observed in man. That is the occurrence of a narrow QRS, its gradual prolongation for one or more additional cycles, and its abrupt return to the narrow form. As a variant of this, one might find a narrow cycle, next a much wider one, and then one or more still wider, but equal QRS complexes of typical bundle-branch block configuration. This sequence of events should repeat in each of these instances, of course. These would represent bundle-branch block of Type I. Another example, here Type II, would be the occurrence of two or more narrow, followed by two or more wide complexes.

The cases herein reported, in which there is an abrupt transition from wide to narrow form, or vice versa (see especially Figs. 1 and 3), clearly represent intraventricular block of Type II and are, so far as we know, the only cases on record which can be proved to belong to that type. Perhaps the critic will be inclined to dispute this point. He will discover that there is usually a very slight slowing of ventricular rate when the improvement in conduction occurs, and will attribute the improvement to that factor. In this he will, no doubt be right. But at the same time, the evidence for block of Type II is unshaken, as is demonstrated by the narrowness of the QRS complexes of normal configuration, as compared with those during the block in Case 1. The latter average at least 0.16 second in duration (confirmed by the three leads) compared with 0.08 for the former. In block of Type I, the slight slowing might occasion a slight change in QRS width, but nothing approaching this degree. This is understandable if we recall that the damaged region will be reached during every cycle by impulses from both sides, and its physiological state will, therefore, remain unchanged. A slight slowing of the heart will not cause a sufficient immediate change in the physiological state to permit such a transition within the time of a single cycle. We are manifestly dealing, therefore, with a Type II block, the only type in which such abrupt changes occur.

The immediate cause of the sudden transition, whether it be alteration in intracardiac blood supply, in pressure, or in some other factor, is not to be regarded as essentially different from the causes of a relatively gradual transition. Under the circumstances of a rather sharply localized region of depression in a bundle-branch, yet one capable of producing block, but causing little or no slowing of the intraventricular impulse, the only possible result of a gradual improvement in the functional condition is an abrupt transition from block to practically undelayed conduction.

In conclusion, we suggest that in those cases of gradual transition from apparently complete bundle-branch block to normal intraventricular conduction, the functional change in the bundle-branch has affected a stretch of tissue of some length. Such a block is, therefore, generally to be regarded as an intraventricular counterpart of A-V block of Type I. Where no transitional complexes occur, but the change is sudden, the defect is the intraventricular counterpart of A-V block of Type II with normal P-R intervals, and the affected stretch of muscle is presumably short.

THEORETICAL CONSIDERATIONS REGARDING THE DANGER OF VENTRICULAR FIBRILLATION IN BUNDLE-BRANCH BLOCK

One of the points stressed in this paper is the increased operative risk during bundle-branch block in those patients in whom the condi-

tion is a transient one. The outstanding danger appears to be ventricular fibrillation.

From the theoretical side it is not difficult to see why the danger is present. The sequential invasion of the two ventricles, the one by the supraventricular impulse, the other by the impulse from the opposite ventricle, means that the former begins its recovery earlier. At the same time the ventricle whose bundle branch is damaged is in part depressed; regions of muscle are presumably present through which conduction is slow. Now if, to the already existing depression, there is added the effect of the anesthetic, conduction of the impulse in some pathway may become slowed still more. Thus, by the time impulse has travelled through this region, the muscle beyond, which was activated relatively early, may have passed out of the absolutely refractory state, and re-entry is possible. With re-entry the impulse can again swing through the same circuit. Ventricular tachycardia (or flutter) progressing rapidly to fibrillation is the consequence. If, to these factors, irreciprocal conduction or unidirectional block be added, the possibility of fibrillation is much easier to understand. Garrey²³ and Mines²⁴ agreed on the importance of one-way block for the establishment of fibrillation, and this view has recently been supported by Schmitt and Erlanger.²⁵

SUMMARY

1. Eight cases of partial bundle-branch block of varying degrees are presented with abstracts of their clinical histories, complete physical and laboratory data and electrocardiographic studies.

2. Three unusual cases of transient Type II, intraventricular or bundle-branch block are recorded with sudden transition from complete bundle-branch block to normal intraventricular conduction times in response to respiratory maneuvers. The possible mechanical or nervous factors concerned in the production of the changes are considered to be anoxemia as well as fatigue. Vagus effect may be contributory.

3. We have stressed especially the importance of the recognition of this transient type of disturbance because of its better prognostic outlook. When present it must be relieved by therapeutic rest before necessary surgical or intravenous procedures are to be undertaken.

4. The increased risk assumed in submitting patients, in the presence of bundle-branch block, to a procedure that may apparently only slightly affect the blood pressure and the heart is emphasized.

5. The theories of partial heart-block with special reference to and the intraventricular counterparts of the accepted Types I and II of auriculoventricular types are discussed at some length.

6. The theoretical reasons for the danger of precipitating fatal ventricular fibrillation in the presence of bundle-branch block are given.

REFERENCES

1. Lewis, T.: Certain Physical Signs of Myocardial Involvement, *Brit. M. J.* 1: 484, 1913.
2. Matthewson, G. D.: Lesions of the Branches of the A-V Bundle, *Heart* 4: 385, 1913.
3. Carter, E. P.: Clinical Observations on Defective Conduction in the Branches of the A-V Bundle, *Arch. Int. Med.* 13: 803, 1914.
4. Robinson, G. C.: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, *Arch. Int. Med.* 18: 830, 1916.
—: The Significance of Abnormalities in the Form of the Electrocardiogram, *Arch. Int. Med.* 24: 422, 1919.
5. Krumbhaar, E. B.: Transient Heart-Block. *Electrocardiographic Studies*, *Arch. Int. Med.* 19: 750, 1917.
6. Willius, F. A., and Kieth, N. M.: Intermittent Incomplete Bundle-Branch Block, *AM. HEART J.* 2: 255, 1927.
7. Von Kapff, D. W.: Ueber einen Fall von Passageren Schenkel-Block, *Klin. Wchnschr.* 7: 357, 1928.
8. Baker, B. M.: The Effect of Cardiac Rate and the Inhalation of Oxygen on Transient Bundle-Branch Block, *Arch. Int. Med.* 45: 814, 1930.
9. Leinbach, R. F., and White, P. D.: Two-to-One Right Bundle-Branch Block, *AM. HEART J.* 3: 422, 1928.
10. Slater, S. R.: Partial Bundle-Branch Block, A Case of Three-to-One and Four-to-One Block, *AM. HEART J.* 5: 617, 1930.
11. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* 16: 1008, 1925.
- 12a. Mobitz, W.: Ueber die unvollständige Störung der Erregungsüberleitung zwischen Vorhof und Kammer des menschlichen Herzens, *Ztschr. f. d. ges. exper. Med.* 41: 180, 1924.
- 12b. Mobitz, W.: Ueber den partiellen Herzblock, *Ztschr. f. klin. Med.* 107: 449, 1928.
13. Scherf, D.: Ueber intraventrikuläre Störungen der Erregungsausbreitung bei den Wenckebachschen Perioden, *Wein. Arch. f. inn. Med.* 18: 403, 1929.
14. Wenckebach, K. F., and Winterberg, H.: Die Unregelmässige Herzthätigkeit, Leipzig, 1927, Wilhelm Engelmann.
15. Wenckebach, K. F.: Beiträge zur Kenntnis der menschlichen Herzthätigkeit, *Arch. f. Anat. u. Physiol., Physiol. Abt.* (Cited from Wenckebach and Winterberg, p. 297), 1906.
16. Hay, J.: Bradycardia and Cardiac Arrhythmia Produced by Depression of Certain of the Functions of the Heart, *Lancet* 84: 139, 1906.
17. Ashman, R., and Herrmann, G. R.: A Supernormal Phase in Conduction and a Recovery Curve for the Human Junctional Tissues, *AM. HEART J.* 1: 594, 1926.
18. Herrmann, G. R., and Ashman, R.: Heart-Block With and Without Convulsive Syncope, *AM. HEART J.* 1: 269, 1926.
19. Scherf, D., and Shookhoff, C.: Reizleitungsstörungen im Bündel. II. Mitteil., *Wien. Arch. f. inn. Med.* 11: 425, 1925.
20. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle-Branch Block and of the Refractory Period of the Heart of the Dog, *Heart* 8: 229, 1921.
21. Wilson, F. N., and Herrmann, G. R.: Some Unusual Disturbances in the Mechanism of the Heart Beat, *Arch. Int. Med.* 31: 923, 1923.
—: Vagus Influences on Form of Electrocardiogram, *ibid.* 16: 1008, 1915.
22. Wolfertli, C. C., and McMillan, T. M.: Observations on the Mechanism of Relatively Short Intervals in Ventriculoauricular and Auriculoventricular Sequential Beats During High Grade Heart-Block, *AM. HEART J.* 4: 521, 1929.
23. Garrey, W. E.: The Nature of Fibrillary Contraction of the Heart. Its Relation to Tissue Mass and Form, *Am. J. Physiol.* 33: 397, 1914.
24. Mines, G. R.: On Circulating Excitations in Heart Muscle and Their Possible Relation to Tachycardia and Fibrillation, *Tr. Roy. Soc. Canada, Series 3*, 8: 43, 1914.
25. Schmitt, F. O., and Erlanger, J.: Directional Differences in Conduction of Impulse Through Heart Muscle and Their Possible Relation to Systolic and Fibrillary Contractions, *Am. J. Physiol.* 87: 326, 1928.

26. Straub, H., and Kleemann, M.: Partiieller Herzblock mit Alternans, *Deutsches Arch. f. klin. Med.* 123: 296, 1917.
27. Stenström: Contributions to the Knowledge of Incomplete Bundle-Branch Block, *Act. med. Scand.* 57: 385, 1923; An Experimental and Clinical Study, *ibid.* 60: 552, 1924; Further Experiences, *ibid.* 67: 353, 1927.
28. Cohn, A. E.: Transient Complete A-V Dissociation Showing Constantly Varying Ventricular Complexes, *Heart* 5: 5, 1913-14.
29. Christian, Henry A.: Transient A-V Dissociation With Varying Complexes Caused by Digitalis, *Arch. Int. Med.* 16: 341, 1915.
30. Palmer, R. S., and White, P. D.: Paroxysmal Ventricular Tachycardia With Rhythmic Alternation in Direction of the Ventricular Complexes in the Electrocardiogram, *AM. HEART J.* 3: 454, 1928.
31. Barnes, A. R., and Yater, W. M.: Paroxysmal Tachycardia and Alternating Incomplete Right and Left Bundle-Branch Block With Fibrosis of the Myocardium, *M. Clin. North America* 12: 1603, 1929.
32. Cohn, A. E., and Lewis, T.: The Pathology of Bundle-Branch Lesions of the Heart, *Proc. New York Path. Soc.* 14: 207, 1914.

OBSERVATIONS ON THE ETIOLOGY AND TREATMENT OF PAROXYSMAL VENTRICULAR TACHYCARDIA*

EDWARD H. SCHWAB, M.D.
GALVESTON, TEXAS

ALTHOUGH the subject of ventricular tachycardia has been exceedingly well studied, the total number of cases reported in the literature has been small. In this communication three additional cases are reported, two of the usual type and one of the alternating bidirectional variety. In one case the paroxysms were associated with persistent atrioventricular rhythm, a combination not previously reported in the literature. In addition, the effectiveness of quinidine therapy in the alternating bidirectional variety of ventricular tachycardia is demonstrated for the first time.

CASE REPORTS

CASE 1.—*Diagnosis: Hypertensive heart disease, congestive heart failure, ventricular tachycardia, digitalis intoxication.* L. B., a negro laborer, 47 years old, entered the John Sealy Hospital January, 1924, because of an acute bronchitis. The routine examination revealed a blood pressure of 160/100 mm. Hg. No cardiac enlargement was demonstrable either by physical examination or by roentgenological study. The urine showed a trace of albumin. He was not seen again until September, 1927, when he re-entered the hospital complaining of shortness of breath and swelling of the feet of about two months' duration. Examination at this time revealed moderate cardiac enlargement, a blowing mitral systolic murmur, enlargement of the liver, moist râles in the base of both lungs, and edema of the lower extremities. The systolic blood pressure ranged from 165 to 180, and the diastolic from 105 to 115. The blood Wassermann was negative. The urine showed a persistently low specific gravity. The blood chemistry was normal. The electrocardiogram showed a moderate degree of left ventricular preponderance, slurring of QRS complexes in all leads, occasional auricular and ventricular premature beats, and inversion of the T-wave in Leads I and II. Following digitalization he made a rapid and satisfactory recovery. Shortly after his discharge he discontinued treatment and began doing hard manual labor on the docks. He re-entered the hospital in October, 1927, in essentially the same condition as on the preceding admission. After a prolonged period of bed rest and the usual therapeutic procedures he improved and was discharged practically free of symptoms. He was seen at irregular intervals in the Out-Patient Department until January, 1928, when he was again hospitalized because of congestive heart failure. On this admission gallop rhythm and alternation of the pulse were noted for the first time. The electrocardiogram showed no significant changes over those taken on previous admissions. The response to treatment was much slower than previously, and after prolonged treatment he was sent home to spend the remainder of his life as a cardiac invalid.

On May 16, 1929, he was brought to the emergency room of the hospital. He appeared to be in great distress. The mental state was that of a stupor, and he

*From the John Sealy Hospital and the Department of Internal Medicine, University of Texas, School of Medicine, Galveston, Texas.

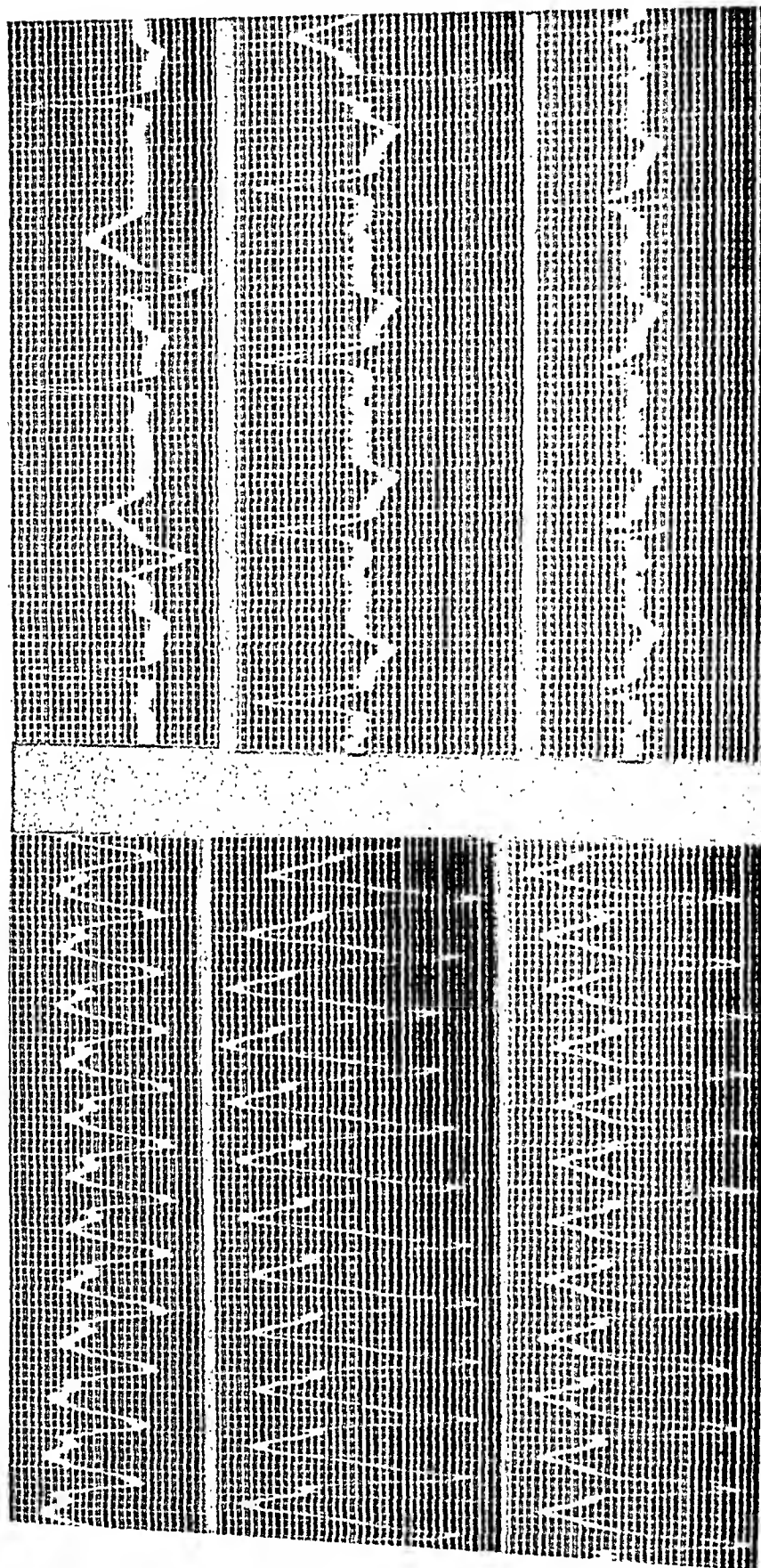


Fig. 1-A.

Fig. 1-A.—Case 1. Three usual leads. Ventricular tachycardia, rate 220. The P-waves are not discernible. (In this and the subsequent electrocardiograms distances between abscissae represent 10-4 volts, and time is in fifths of a second.)

Fig. 1-B.

Fig. 1-B.—Case 1. Three usual leads. Curve taken after period of tachycardia showing normal mechanism with frequent ectopic ventricular beats. The shape of the premature ventricular complex is similar to those occurring during the paroxysm.

could be aroused only with difficulty. The pulse was imperceptible at the wrist. The blood pressure was too low to be taken. On auscultation of the heart the rate was found to be above 200, apparently quite regular, but there seemed to be some variation in the intensity of the individual heart sounds. Moist râles were heard throughout the chest. Six mg. of strophanthin were given intravenously without any apparent effect. The electrocardiogram showed a ventricular tachycardia with a rate of 220 (Fig. 1 A). At 10:30 o'clock, 0.3 gm. of quinidine sulphate was given by mouth, followed by 0.6 gm. at 11 o'clock. There was a sudden return to normal rhythm at 11:20 o'clock. The rate was 75, regular except for an occasional premature beat, and the blood pressure was 105/80 mm. (Fig. 1B). After recovery he stated that he had been having similar attacks for about one month. He had been taking digitalis at irregular intervals for the past six weeks. The attacks came on suddenly without apparent cause, lasted from a few minutes to several hours and ceased quite abruptly. During the attacks he said that he

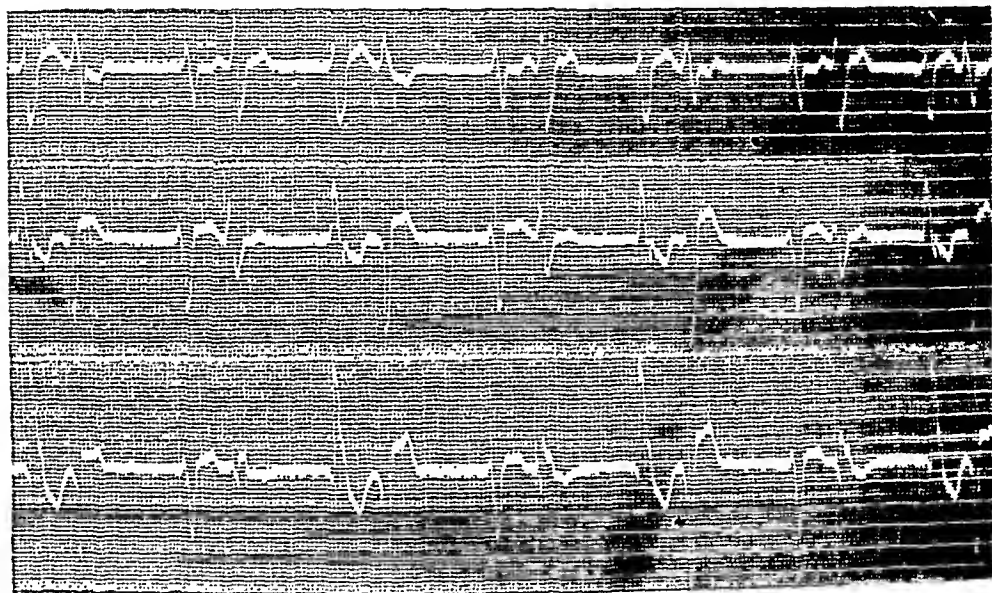


Fig. 2.—Case 1. Leads I, II, and III. Curve taken following digitalis intoxication. Auricular fibrillation is present with complete heart-block and idioventricular rhythm. The ectopic beats appear in couples and in the majority of cases show alternation in direction.

became quite short of breath, very weak, and had a feeling of constriction in his chest. The paroxysm which brought him to the hospital had lasted eighteen hours.

For two or three days following the attack the pulse was quite irregular, due to many premature beats which occasionally produced a bigeminy. There was no edema present. He was placed on 0.6 gm. of quinidine sulphate daily. After a few days the pulse became quite regular. On May 29, 1929, while taking a bath, he had another paroxysm which lasted about an hour. The curves taken at that time were identical with the former ones. He was given 0.6 gm. of quinidine sulphate by mouth, and the paroxysm ceased twenty minutes later. On June 6, 1929, he suffered another attack which lasted about fifteen minutes. The quinidine was increased to 1.3 gm. daily. His general condition had improved a great deal, and he was discharged from the hospital and advised to continue taking 1.3 gm. of quinidine daily. On June 25, 1930, he appeared in the clinic and stated that he had suffered no more attacks but that he had become very short of breath. He had been taking the quinidine as prescribed. Examination showed the patient to be very

dyspneic, the liver was greatly enlarged, and there was a pitting edema extending well above the knees. The pulse was regular, rate 96, and alternation was present. The blood pressure was 168/105 mm. Hg. He was given a prescription for thirty 0.1 gm. tablets of the powdered leaf of digitalis and advised to take two tablets four times daily until fourteen had been taken and then to return for observation. After returning home his condition became much worse, and instead of returning to the hospital he continued taking the digitalis until he had exhausted his supply, i.e., 3 gm. of the powdered leaf of digitalis in less than four days. He was brought to the emergency room June 30, 1930, in a paroxysm which had lasted four hours. It ceased a few minutes after taking an electrocardiogram which was identical with those taken previously during the paroxysms. He stated that he had been having five to six attacks daily since the second day after he began taking digitalis. An electrocardiogram taken after the paroxysm revealed the following: auricular fibrillation, complete heart-block, and idioventricular rhythm (Fig. 2). Quinidine sulphate was administered in doses of 0.6 gm. every four hours. He had one paroxysm during the night which lasted only a few minutes. Dyspnea was marked, and a generalized anasarca was present. He died suddenly the following morning.

Autopsy Findings.—The heart weighed 950 gm. There were a few adhesions between the left ventricle posteriorly and the parietal pericardium. There was marked dilatation of the right side of the heart. The left ventricular wall was three centimeters in thickness. The valves showed no significant changes. In the tip of the left ventricle near the endocardial surface a healed infarct one centimeter in diameter was found. The first part of the aorta showed some dilatation and a few atheromatous plaques. The coronary arteries were moderately thickened and tortuous. Microscopically, the kidneys showed evidence of a chronic diffuse nephritis.

The curves taken during the paroxysms of tachycardia in this case do not fulfill all the criteria cited by Robinson and Herrmann,¹ as the P-waves are not distinguishable. However, the form of the ectopic beats seen in the curve taken after cessation of the paroxysm are similar to those ventricular complexes seen during the rapid rate. In addition, the clinical course of the tachycardia and the effectiveness of quinidine therapy establish the diagnosis, and readily differentiate it from the condition with which it most likely would be confused, namely, auricular flutter with a one to one response. The curve (Fig. 2) taken following the severe digitalis intoxication is quite unusual. Auricular fibrillation is undoubtedly present with, perhaps, complete auriculo-ventricular block, as none of the ventricular complexes conform to the supraventricular type. Four different types of ventricular complexes are seen, each recurring at perfectly regular intervals. The complexes appear in couples and show alternation in direction in the majority of instances. The rôle of digitalis as a precipitating factor of the paroxysms of ventricular tachycardia in this case cannot be questioned. The condition had been perfectly controlled by quinidine for several weeks, the paroxysms reappearing shortly after the institution of digitalization, and increasing greatly in frequency as the administration of the drug was continued.

CASE 2.—Diagnosis: Hypertensive heart disease, congestive heart failure, coronary occlusion, chronic uremia, ventricular tachycardia. E. B., a white man, fifty-four years old, an engineer by occupation, entered the hospital June 22, 1930, complaining of shortness of breath and swelling of the feet. These symptoms first appeared about seven months ago and had been progressively becoming worse. He had been told by several physicians that his blood pressure was over 200. Four nights before coming to the hospital he had a severe attack of dyspnea associated with intense precordial pain. The pain was most intense over the lower end of the sternum and under the left scapula. This pain persisted for about four hours. Since this attack his condition had become much worse, and of late he had been having severe

headaches and attacks of intractable vomiting. The past history was irrelevant. The family history was interesting in that his father, mother, and one sister had died of kidney trouble.

On physical examination the patient was quite dyspneic. The heart was greatly enlarged. A moderately loud blowing systolic murmur was heard at the apex. The pulse was quite irregular due to many premature beats, which occasionally produced long runs of bigeminy. The blood pressure was 140/80 mm. Hg. The peripheral



Fig. 3.—Case 2. Three usual leads, upper two strips are Lead I. The offset and onset of a paroxysm of ventricular tachycardia are shown in the second strip. The rate (taken from another portion of the record) is 160. Atrioventricular rhythm is present. There is some evidence of retrograde heart-block. Note the marked inversion of the T-waves in the first two leads.

vessels were markedly sclerosed and showed some beading. The liver was greatly enlarged, and there was some ascites present. Moist râles were heard over the chest posteriorly. There was a pitting edema of the lower extremities. The routine blood count revealed a marked secondary anemia. The blood urea was 100 mg., and the creatinine was 7.5 mg. per 100 c.c. of blood.

The patient had been under the treatment of a physician in the city for several months and was taking digitalis up to the time of admission to the hospital, how-

ever, it was impossible to ascertain the amount that he had taken. The day following admission it was noticed that in addition to the many premature beats, there were short paroxysms of tachycardia lasting from a few seconds to as long as thirty minutes. The rate during the paroxysms was approximately 150, and the rhythm showed a slight irregularity. The onset and offset were abrupt. Vagal stimulation had no effect on the rate. An electrocardiogram showed atrio-ventricular rhythm with runs of ventricular tachycardia during which the rate was 160 (Fig. 3). He was immediately placed upon 0.75 gm. of quinidine sulphate daily. The premature beats decreased greatly in number, and no more paroxysms of tachycardia were noted. Subsequent curves taken revealed only occasional ventricular premature beats; however, the atrio-ventricular rhythm persisted. In spite of treatment his general condition became rapidly worse, and he died a week later in uremic coma, the terminal event being a hypostatic pneumonia. Autopsy was refused.

The rôle of digitalis in the production of the arrhythmia in this case is not quite so evident as in the other cases, although it was apparently a factor. The patient had been taking digitalis for some time, but it was impossible to ascertain the exact amount taken. Atrio-ventricular rhythm is known to occur occasionally as a result of digitalis administration, but it is not generally thought of as being a toxic manifestation of the drug. The runs of bigeminy noted on admission offer further evidence that he had probably received too much of the drug. The history of the sudden onset of severe precordial pain, the prostration, the fall in blood pressure, and the progressive heart failure furnish sufficient clinical grounds for the diagnosis of coronary occlusion. The marked inversion and the character of the T-waves would tend to confirm this diagnosis.

CASE 3.—*Diagnosis: Syphilitic heart disease (?), aortic regurgitation, congestive heart failure, auricular fibrillation, ventricular tachycardia.* K. C., a white man, sixty-five years old, a watchman by occupation, was sent into the John Sealy Hospital March 28, 1929, complaining of intense cramping pain in the lower part of the abdomen. Examination revealed a strangulated left inguinal hernia. A careful cardiac examination was not done at that time. He was immediately subjected to a surgical operation, the strangulation relieved and the hernia repaired. Local anesthesia (novocaine) was employed. Post-operative recovery was uneventful, and he was discharged three weeks later in good condition.

He returned to the hospital June 27, 1929, complaining of shortness of breath and swelling of the feet which began two weeks previously, and which had become progressively worse. The family history was irrelevant. Twenty years previously he had had a bad attack of gonorrhea which was followed by a stricture of the urethra. He denied ever having had a penile sore. On physical examination there was some obesity. Dyspnea was marked. The chest was quite emphysematous. The heart was greatly enlarged downward and to the left. On auscultation there was heard at the aortic area a soft to-and-fro murmur. The heart rate was rapid and quite irregular, due to many premature beats. The blood pressure was 150/65 mm. Hg. A moderate amount of arteriosclerosis of the diffuse type was present. Moist râles were heard over the entire chest, the liver was enlarged and tender, and a pitting edema extended well up the thighs. The electrocardiogram showed sinus rhythm, slurring of the QRS complexes in all leads, inversion of the T-wave in Leads I and II, and ventricular premature beats. Following digitalization and rest in bed the symptoms and the edema disappeared. He was discharged July 7, 1929, and advised to continue taking a maintenance dose of digitalis.

He returned to the Out-Patient Department at regular intervals for observation. He remained fairly well until February 17, 1930, when it was necessary to hospitalize him again because of congestive heart failure. On this admission the physical examination was essentially the same except that the degree of failure was more

marked. The blood pressure was 150/80 mm. Hg. Alternation of the pulse was noted. As before, the pulse was quite irregular due to many premature beats. An electrocardiogram was similar to that taken on the previous admission (Fig. 4). The blood urea nitrogen was within normal limits. The blood Wassermann was frankly negative. It was necessary to resort to the use of the mercurial diuretics to mobilize the edema. After three weeks of energetic treatment he was discharged edema-free, but the dyspnea, though lessened, still remained.

He returned to the hospital two weeks later again showing marked dyspnea and edema. Examination May 5, 1930, revealed a generalized anasarca. The pulse was still irregular because of many premature beats, and the blood pressure was 140/68 mm. Hg. Intense pulmonary congestion was evident. He had been taking 0.1 gm. of the powdered leaf of digitalis daily since the last dismissal from the hospital. The interne was not cognizant of this fact, and from May 5 to May 18, he received 3 gm. of the powdered leaf of digitalis. The electrocardiogram on admission showed sinus rhythm, whereas a curve taken on May 19, 1930, showed auricular fibrillation

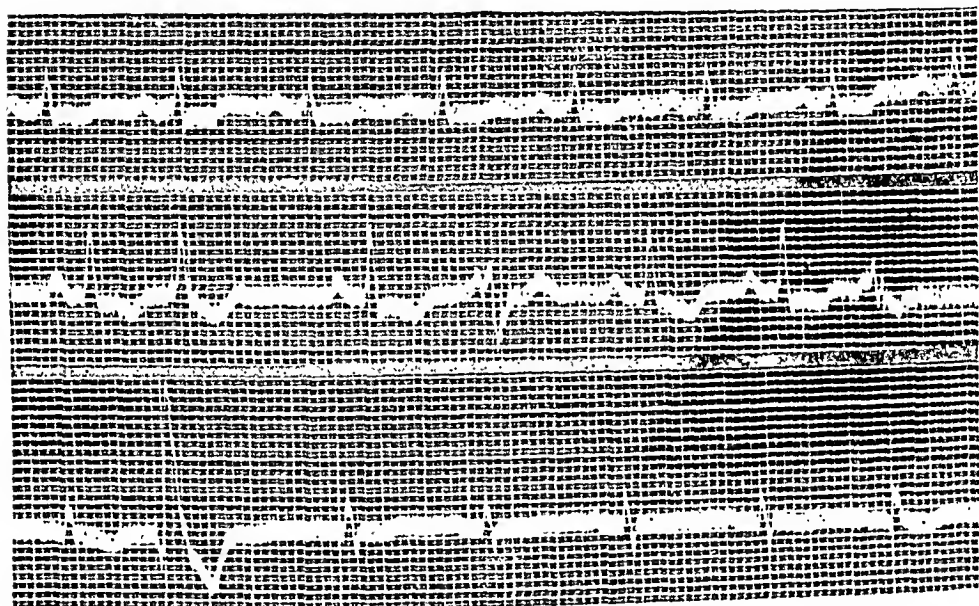


Fig. 4.—Case 3. Three usual leads. Record obtained on February 17, 1930. Sinus rhythm is present with frequent ectopic beats. There is slurring of the ventricular complexes in all leads. The T-waves in Leads I and II are inverted.

with ventricular premature beats producing a bigeminy (Fig. 5A). A tracing taken the following day revealed paroxysms of alternating bidirectional ventricular tachycardia (Fig. 5B). The next day the frequency and the duration of the paroxysms increased. One paroxysm was observed to last three hours. The digitalis was immediately discontinued and the administration of quinidine sulphate begun, in doses of 0.6 gm. daily. This was increased the following day to 1 gm. daily. Six hours after the quinidine was started the paroxysm ceased and numerous observations failed to reveal any reappearance; however, the auricular fibrillation along with occasional ectopic ventricular beats persisted. The patient showed no response to treatment, the edema being exceedingly obstinate. A few days before death he developed marked mental symptoms. Death occurred May 27, 1930. Autopsy was refused.

On admission this patient was apparently fully digitalized, as he had been taking a maintenance dose of digitalis for several weeks prior to his final entry. When he entered the hospital, sinus rhythm was present along with many ectopic ventricular beats. Due to an oversight he was given digitalis in sufficient amounts again fully

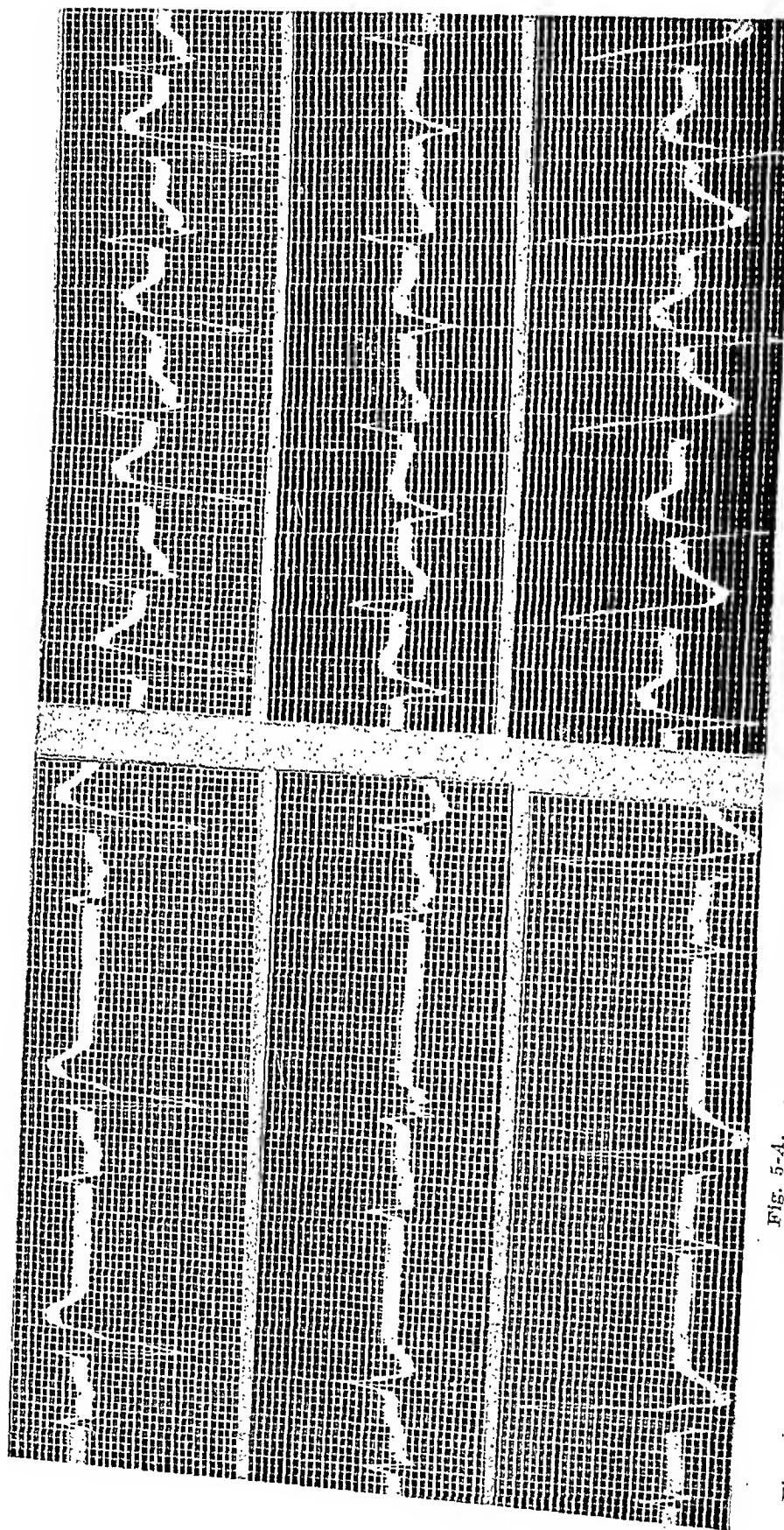


Fig. 5-4.

Fig. 5-4.—Case 3. Leads I, II and III. Record obtained May 19, 1930, showing auricular fibrillation with ventricular premature beats producing a bigeminy.

Fig. 5-B.

Fig. 5-B.—Case 3. Three usual leads. Record obtained May 20, 1930. Alternating bidirectional ventricular tachycardia with a rate of 140. In addition to the alternation in direction of the ventricular complexes there is predominantly alternation in the length of cycles.

to bring him under the influence of the drug. Auricular fibrillation appeared after a short time, and was undoubtedly a manifestation of digitalis intoxication. The associated bigeminy would tend to substantiate this contention. Shortly thereafter, the appearance of the paroxysms of ventricular tachycardia were noted. As in the cases reported by Palmer and White² there is not only alternation in the direction of the ventricular complexes, but there is also predominantly alternation in the length of the cycles, the interval between an inverted and an upright complex being shorter than that following an upright complex in Leads I and II, whereas the reverse holds true in Lead III. It is interesting to note that the majority of the cases of alternating bidirectional ventricular tachycardia reported were associated with auricular fibrillation.

DISCUSSION

No definite proof has as yet been advanced as to the underlying mechanism in ventricular tachycardia. For the unidirectional type, most writers advance the theory that the mechanism is similar to that which is generally conceded to produce paroxysmal auricular tachycardia, namely, a single irritable ectopic focus. The two types of tachycardia are similar in that the onset and offset of the abnormal rhythm are abrupt and bear the same relationship to the normal rhythm as do single ectopic beats. The great point of difference, however, is that the action of the heart during paroxysms of auricular tachycardia is notable for its regularity, whereas in the ventricular type, as emphasized by Strong and Levine,³ a slight but noticeable irregularity occurs. Largely because of this irregularity, and because of the therapeutic response of the condition to quinidine, Levine and Fulton⁴ have suggested that the underlying mechanism is a circus movement similar to that seen in the auricle in auricular fibrillation and flutter. The variation in the configuration of the abnormal complexes, which is commonly seen, could be explained on a basis of aberration; nevertheless, it is more logical to assume that it is a result of a variance of the path assumed by the circus, which likewise explains the slight irregularity in rhythm.² The unusual curve (Fig. 2) taken in Case 1, following the digitalis intoxication, could possibly be due to a circus movement similar to that producing the paroxysms of tachycardia, its path being greatly altered by changes in the refractory period of the heart muscle, a result of the toxic effect of the digitalis. The possible mechanisms underlying the alternating bidirectional type of ventricular tachycardia have been discussed in detail in the literature.^{2, 5} The double ventricular circus movement as suggested by Palmer and White seems most likely, as the condition cannot be adequately explained on the basis of a single circus. Clinically, the two types are identical and can be separated only by electrocardiographic study.

The majority of the cases of ventricular tachycardia have occurred in individuals with advanced heart disease, most of them being in a state of congestive or anginal failure at the time of the onset of the arrhythmia. However, several cases are on record in which no abnor-

mal cardiac findings were demonstrable. The alternating bidirectional variety occurs with greater uniformity in patients with grave forms of heart disease than does the unidirectional type. In all of the cases of the alternating bidirectional form reported, pathological change in the heart was noted; in one instance the only finding was cardiac enlargement, the remainder showed evidence of marked structural cardiac disease. Advanced coronary artery disease and coronary occlusion are important predisposing factors. Coronary occlusion was present in eight out of the ten cases in one series.⁴ In approximately one-fourth of the cases reported, cardiac infarction had preceded the onset of the ventricular tachycardia. In patients in whom no organic heart disease is present, the prognosis is essentially good; in those in whom definite organic changes are evident, the prognosis is grave, especially if the alternating bidirectional form of tachycardia is present, the majority of these patients dying in from a few hours to a few weeks.

The relationship of digitalis to the occurrence of ventricular tachycardia has been emphasized by a great many writers on the subject.^{6, 7, 8, 9, 10, 11, 12} It undoubtedly plays a very important part, acting largely as the precipitating or exciting factor. Considering all of the cases of both types, the drug had been administered prior to the onset of the arrhythmia in approximately 50 per cent of the cases, and in the majority of these, it was given in excessive amounts. In Case 1 of this group, in which the paroxysms had been completely controlled by quinidine, there was a reappearance shortly after the institution of digitalization, and they increased greatly in frequency and duration as the administration of digitalis was continued. In one of the cases reported by Gilekrist,¹² Case 2, the frequency of the paroxysms was greatly increased by the giving of digitalis. In Cases 2 and 3 of Levine and Fulton's series, the giving of digitalis caused an increase in the rate of the tachycardia, and a similar experience was reported by Orsi and Villa.¹³ To the contrary, in the case reported by Hart¹⁴ "small doses of digitalis" caused no recurrence; Wolferth and McMillan,¹⁵ Cases 2 and 3, gave digitalis in full doses after the cessation of the paroxysm without apparent effect as regards recurrence.

The rôle of digitalis as an exciting factor in the causation of ventricular tachycardia is much more apparent after a study of the reported cases of the alternating bidirectional type. Including the case herewith reported there are twenty-two cases recorded in the literature.^{2, 5, 6, 7, 8, 9, 12, 13, 16, 17, 18} Of this number, excluding three of Galavardin's cases¹⁶ in which the records are not clear, all but two cases had received digitalis. Of these seventeen cases, fifteen were said to have received the drug in toxic amounts. In the case of this type reported here, digitalis had been given in sufficient amounts to convert sinus rhythm to auricular fibrillation. In the case reported by Orsi

and Villa,¹³ a change from the usual type of ventricular tachycardia to the alternating bidirectional form occurred a few seconds following the intravenous injection of calcium chloride.

Despite the fact that evidence has been adduced to show that quinidine itself may cause ventricular tachycardia,^{19, 20, 21, 22} the drug apparently has a specific effect in terminating the paroxysms of tachycardia and preventing their recurrence. In all the cases reported in which the drug has been used, uniform success has been attained. The drug is apparently just as specific in controlling the alternating bidirectional variety as in the usual type, although no definite conclusions can be drawn from its use in a single case. The amount of the drug necessary to produce therapeutic results varies greatly from case to case. On the whole, somewhat larger doses are needed to terminate a paroxysm than is necessary to prevent the recurrence of paroxysms. Very large maintenance doses of the drug have been given over long periods of time without any ill effects. In those cases in which the patient's condition is critical, it is perhaps best to administer the drug intravenously, although its action by mouth is quite prompt.

SUMMARY AND CONCLUSIONS

1. Three cases of paroxysmal ventricular tachycardia are reported, two of the usual variety and one of the alternating bidirectional type.

2. All three cases were treated with quinidine with uniform success in controlling the arrhythmia.

3. Digitalis, especially when given in excessive amounts, is apparently an exciting factor in the production of ventricular tachycardia. The association is much closer in the alternating bidirectional variety than in the unidirectional form.

4. Because of the close association between coronary occlusion, digitalis, and ventricular tachycardia, digitalis should be administered with extreme caution to patients who give a history of a recent cardiac infarction.

NOTE.—The author is indebted to Dr. R. S. Palmer and other members of the Cardiographic Laboratory of the Massachusetts General Hospital, Boston, and to Dr. George R. Herrmann of New Orleans, for valuable help in the interpretation of the curves from Case 1.

REFERENCES

1. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, *Heart*, 8: 59, 1921.
2. Palmer, R. S., and White, P. D.: Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of the Ventricular Complexes in the Electrocardiogram, *AM. HEART J.*, 3: 454, 1928.
3. Strong, G. F., and Levine, S. A.: Irregularity of Ventricular Rate in Paroxysmal Ventricular Tachycardia, *Heart*, 10: 125, 1923.
4. Levine, S. A., and Fulton, M. N.: The Effect of Quinidine Sulphate on Ventricular Tachycardia: Clinical Observations, *J. A. M. A.*, 92: 1162, 1929.
5. Marvin, H. M.: Paroxysmal Ventricular Tachycardia with Alternating Complexes Due to Digitalis Intoxication, *AM. HEART J.*, 4: 21, 1928.

6. Reid, W. D.: Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, *Arch. Int. Med.* 33: 23, 1924.
7. Luten, D.: Clinical Studies of Digitalis: II. Toxic Rhythms, *Arch. Int. Med.*, 35: 74, 1925; *Advanced Toxic Rhythms*, *Ibid.*, p. 87.
8. Schwensen, C.: Ventricular Tachycardia as a Result of the Administration of Digitalis, *Heart*, 9: 199, 1922.
9. Smith, W. C.: Ventricular Tachycardia Showing Bi-directional Electrocardiograms, Associated with Digitalis Therapy, *AM. HEART J.* 3: 723, 1928.
10. Howard, T.: Double Tachycardia: Coexisting Auricular and Ventricular Due to Digitalis, *Am. J. Med. Sc.* 173: 165, 1927.
11. Danielopolu, D.: Tachycardia paroxystique provoquée chez l'homme par la digitale et la strophantin, *Arch. d. mal. du coeur*, 15: 537, 1922.
12. Gilchrist, A. R.: Paroxysmal Ventricular Tachycardia, *AM. HEART J.*, 1: 546, 1926.
13. Orsi, A., and Villa, L.: Sur l'amarchie ventriculaire, *Arch. d. mal. du coeur*, 21: 353, 1928.
14. Hart, T. S.: Paroxysmal Tachycardia, *Heart*, 4: 128, 1913.
15. Wolferth, C. C., and McMillan, T. M.: Paroxysmal Ventricular Tachycardia: Report of One Case with Normal Mechanism and Three with Auricular Fibrillation, *Arch. Int. Med.*, 31: 184, 1923.
16. Gallavardin, L.: Tachycardie ventriculaire terminale: Complexes alternantes on multiformes, *Arch. d. mal. du coeur*, 19: 153, 1926.
17. Felberbaum, D.: Paroxysmal Ventricular Tachycardia: Report of Unusual Type, *Am. J. M. Sc.*, 166: 211, 1923.
18. Strauss, M. B.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.*, 179: 337, 1930.
19. Wilson, F. N.: Disorders of the Heart Beat, *Blumer's Bedside Diagnosis*, W. B. Saunders Co., Vol. II, 647, 1928.
20. Levy, R. L.: Clinical Studies of Quinidine: II. Alternations in the Cardiac Mechanism After Administration of Quinidine to Patients with Auricular Fibrillation with Considerations of Certain Toxic Effects of the Drug, *Arch. Int. Med.*, 30: 451, 1922.
21. Levy, R. L.: Clinical Studies of Quinidine: III. Some Results of the Quinidine Treatment of the Auricular Fibrillation, *New York State J. Med.*, 22: 276, 1922.
22. Lewis, Thomas: The Value of Quinidine in Cases of Auricular Fibrillation and Methods of Studying the Clinical Reaction, *Am. J. M. Sc.*, 73: 781, 1922.

THE EFFECT OF VENTRICULAR EXTRASYSTOLES ON THE A-V CONDUCTION TIME OF THE NEXT AURICULAR IMPULSE*†

ERNEST BLOOMFIELD ZEISLER, M.D.
CHICAGO, ILL.

IT IS fairly common for the A-V conduction time of the auricular impulse directly following a ventricular extrasystole to be prolonged. A case is here presented in which this phenomenon was quite prominent. This was analyzed in an essentially quantitative manner, because otherwise the nature of the phenomenon could not be thoroughly understood.

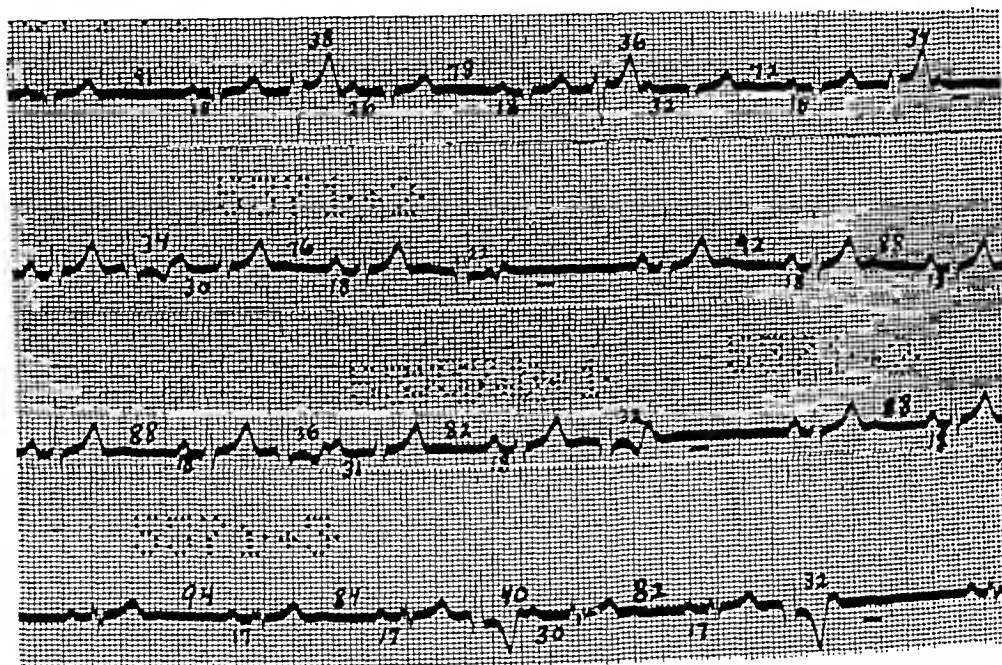


Fig. 1.—Leads I, II, II, and III of Curve 1.

TABLE I (FOR FIG. 1)

| | POST EXTRASYSTOLIC | | | | | | | | | | | | | | | |
|-----|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| R-P | .94 | .92 | .91 | .88 | .88 | .88 | .84 | .82 | .82 | .78 | .76 | .72 | .40 | .38 | .36 | .36 |
| P-R | .17 | .18 | .18 | .18 | .18 | .18 | .17 | .17 | .18 | .18 | .18 | .18 | .30 | .26 | .31 | .32 |

Fig. 1 shows portions of a curve with frequent right ventricular extrasystoles, after which the next auricular impulse is conducted either more slowly or not at all. This partial—and occasionally com-

*From the Heart Station, Michael Reese Hospital, Chicago, Ill.

†Aided by the Emil and Fannie K. Wedeles Fund for the Study and Investigation of Diseases of the Heart and Circulation.

plete—A-V block is explained as follows: The impulse of the ventricular extrasystole is conducted backward through the common bundle to the A-V node. It is not conducted past the node to the auricle (this would be a retrograde ventricular extrasystole, which has never been proved to occur), but it does renew the refractory period of the node, so that the next auricular impulse finds the node either relatively or absolutely refractory and is accordingly either partially or completely blocked. We place the block in the node rather than in the bundle because the refractory period is normally longer in the node and block is more readily produced there.¹

The A-V conduction time of every beat depends upon four things: (1) the presence or absence of organic disease of the A-V node or bundle; (2) the alteration of the A-V node or bundle by drugs or other chemical influences; (3) vagus and sympathetic influences *at the time of passage of the impulse through the node*; and (4) the time permit-

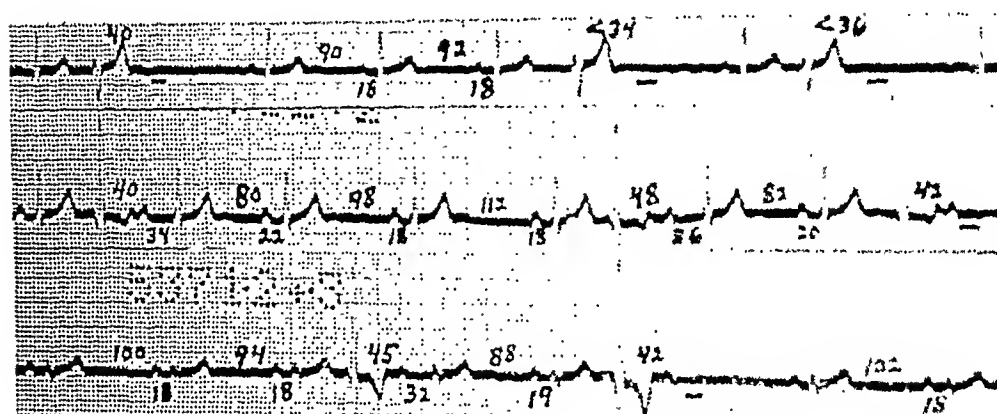


Fig. 2.—Leads I, II, and III of Curve 2, taken two days after Curve 1.

TABLE II (FOR FIG. 2)

| | POST EXTRASYSTOLIC | | | | | | | | | | | | | | | | |
|-----|--------------------|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| R-P | 1.12 | 1.02 | 1.00 | .98 | .94 | .92 | .90 | .88 | .82 | .80 | .48 | .45 | .42 | .42 | .40 | .40 | <.36 |
| P-R | .18 | .18 | .18 | .18 | .18 | .18 | .19 | .20 | .22 | .30 | .32 | - | - | .34 | - | - | - |

ted for recovery of the node after the passage of the last preceding impulse. This time interval, which is called the *recovery time*, is measured from the beginning of the preceding QRS complex to the beginning of the P-wave, and is designated by R-P. Other things being equal, the conduction time increases monotonically as the recovery time decreases;² but, as is well known, even with a long recovery time conduction may be slowed by nervous influences.

To illustrate these principles I have marked on the electrocardiograms shown in Figs. 1, 2 and 3, the recovery times above the curve and the P-R intervals below. Where the P-wave is partly buried in the T-wave, only an upper limit can be determined for the recovery time; when a beat is completely blocked, the P-R interval is indicated by a

dash. The measurements are tabulated in decreasing values of the recovery time as follows:

It is seen that in general the P-R interval increases as the recovery time decreases; the exceptions most probably indicate temporary changes in tonus of the cardiac efferent nerves. On the whole, A-V conduction is slower in Curve 2 than in Curve 1.

To find out what part of the delayed conduction is due to vagus tone we gave the patient $\frac{1}{50}$ gr. of atropine sulphate hypodermically just after Curve 2 was taken; thirty minutes later Curve 3 was taken. The sinus rate was increased only slightly (from 55 to 59). We see again the same general rule for increase of the P-R interval with decrease of the recovery time:

Whereas before atropine, complete block occurred with a recovery time as long as 0.42 sec., after atropine, there is no instance of complete block until the recovery time is as short as 0.20 sec. Similarly,

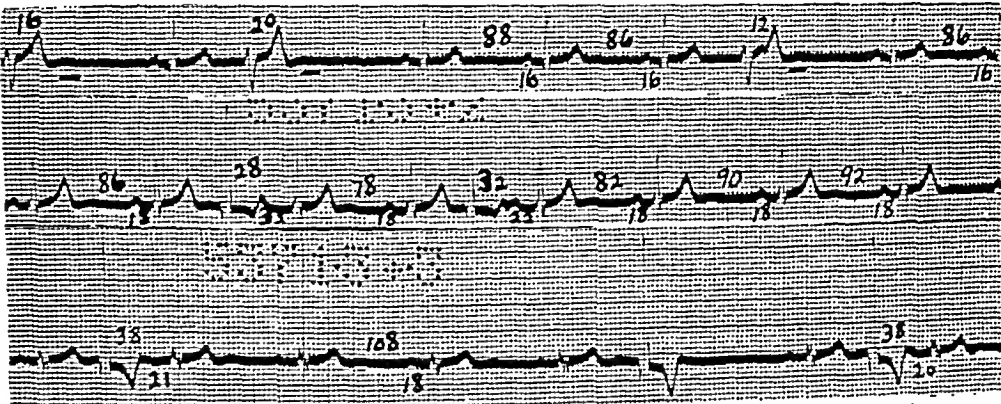


Fig. 3.—Leads I, II, and III of Curve 3, taken on the same day as Curve 2, thirty minutes after atropine.

TABLE III (FOR FIG. 3)

| | | | | | | | | | | | POST EXTRASYSTOLIC | | | | | | |
|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|--------------------|-----|-----|-----|-----|-----|--|
| R-P | 1.08 | .92 | .90 | .88 | .86 | .86 | .86 | .82 | .78 | .38 | .38 | .32 | .28 | .20 | .16 | .12 | |
| P-R | .18 | .18 | .18 | .16 | .16 | .16 | .18 | .18 | .18 | .20 | .21 | .22 | .32 | - | - | - | |

before atropine we have a P-R of 0.36 sec. with a recovery time as long as 0.42 sec. and after atropine a P-R of only 0.20 sec. with a recovery time as short as 0.38 sec. Thus A-V conduction is greatly improved after atropine. After atropine there is no delay in conduction beyond normal limits (0.22) until the recovery time is reduced to 0.28 sec. or less than half the recovery time (0.65 sec.) at normal sinus rhythm (rate 72, PR = 0.18), and there is no complete block until the recovery time is reduced to 0.20 sec. or less than one-third the normal. This marked improvement in conduction indicates that the A-V block before atropine was due to vagus influence and not to organic disease. To rule out a possible sympathetic depression adrenalin was injected

on a subsequent day; this had no effect on the block, so that it appears to have been the vagus which was the controlling factor, though the patient had had no digitalis or other vagus stimulant.

These observations indicate that the effect of a ventricular extrasystole on the A-V conduction of the next auricular impulse is no different in nature from the effect of an auricular extrasystole with the same recovery time on its own A-V conduction. It follows that *complete block of the auricular impulse directly following a late ventricular extrasystole has the same significance as a blocked early auricular extrasystole.*

I wish to express my thanks to Dr. Louis N. Katz for his helpful discussion and his valuable criticism.

REFERENCES

1. Lewis, T.: Quart. J. Med., 14: 339, 1921.
2. Lewis, T., and Master, A. M.: Heart, 12: 209, 1925.

Department of Clinical Reports

A CASE OF MALIGNANT ENDOCARDITIS (PNEUMOCOCCAL), WITH EARLY CALCIFICATION AND WITH CALCAREOUS RENAL EMBOLI

E. R. CULLINAN, M.D., AND W. S. BAXTER, B.A.
LONDON, ENG.

THIS case is recorded for two reasons.

First, it shows the great rapidity with which calcification can take place in newly-formed vegetations on an infected heart valve.

The second point of interest is the presence in the arterioles of the kidney of calcified emboli. These have caused, not infarction by occlusion, but hemorrhage by trauma in the neighboring renal substance.

Whereas it is always assumed that emboli in cases of malignant endocarditis come from vegetations on the heart valves, it is a difficult thing to demonstrate. In this instance, however, there can be little doubt as to the cardiac origin of the calcareous material in the vessels of the kidney.

The patient, a youth of 19 years, was admitted to St. Bartholomew's Hospital, London, on April 23, 1930, with a twenty-four hours' history of malaise, fever, headache, and some mental confusion. He complained chiefly of pain in the back.

On examination, the chest showed impairment of movement, percussion note and air-entry all over the right side, but no added sounds.

The heart was considerably enlarged; mitral and aortic regurgitant murmurs were present, but no presystolic murmur.

The general appearance of the patient and his temperature chart (T:101.4° F., P:96, R:32), together with the chest signs, led to a diagnosis of lobar pneumonia.

There was a vague history of rheumatic disease in childhood which might have accounted for the heart signs.

During the following three days the lung signs on the right side cleared up, but the patient did not feel any better, although the chart on the evening of the fourth day suggested a crisis. On the fifth day he had his first rigor. Rigors followed at the rate of 2 or 3 daily. A few days later the patient complained of transient joint pains and occasional numbness of the extremities. The heart sounds were found to alter slightly from day to day. Blood culture was made on the ninth day and grew pneumococci (Type III). Sudden mistiness of vision in the right eye occurred and retinosecopy showed a pale quadrant in the fundus. Petechiae began to appear and became very numerous on the neck and chest: in a few days the body was covered with them. Red blood cells in abundance now began to appear in the urinary deposit. The patient's mental condition became rapidly worse: drowsiness, low delirium and an almost "Parkinsonian" facies. There was increasing pallor.

A course of mercurochrome injections was begun without benefit, and death occurred on May 13, on the twenty-third day of the illness.

The spleen was not palpable at any stage of the disease and there were no painful nodes in the fingers.

At autopsy, the body was that of a well-covered youth.

There were numerous petechiae over the skin, especially about the shoulders.

Internally, minute hemorrhages were seen on the meninges, the trachea, the pleurae, the pericardium, the peritoneum, and the capsules of the kidneys.

The lungs, both macroscopically and microscopically, showed congestion.

The heart: The pericardium contained about 100 c.c. clear fluid. There were dilatation and hypertrophy of all the chambers. The mitral valve showed past and recent disease. The bases of the valve were thick and fibrosed from old damage, but superimposed on these were recent friable vegetations, which had almost destroyed the cusps. These vegetations were large and cauliflower-like, one being about 2 cm. in diameter (see Fig. 1). They spread from the mitral valve to the wall of



Fig. 1.—A recent vegetation on the mitral valve showing areas of calcification (photograph by A. V. Cobbett).

the auricle, down the chordae tendineae, many of which were eroded, and along the wall of the ventricle to the aortic valve. The latter showed minute recent vegetations and fenestration, but no old scarring.

The most striking feature of the mitral vegetations was the presence of small calcified areas on their surfaces. The rapidity with which these calcified areas must have formed may be judged from the history of the case.

The liver was large and "greasy" and showed microscopically congestion and fatty degeneration.

The spleen was large and soft, and a large number of recent pale infarcts were seen raised above the surface.

The kidneys also contained pale infarcts, but there were in addition many small areas of hemorrhage. Histological examination of these areas showed that the small vessels, and even the glomeruli, in the neighborhood of these hemorrhages contained

particles of calcified material. These particles lay actually within, but not actually blocking, the lumina of the vessels and presumably came from the fragile, partially calcified vegetations on the mitral valve (see Figs. 2 and 3).

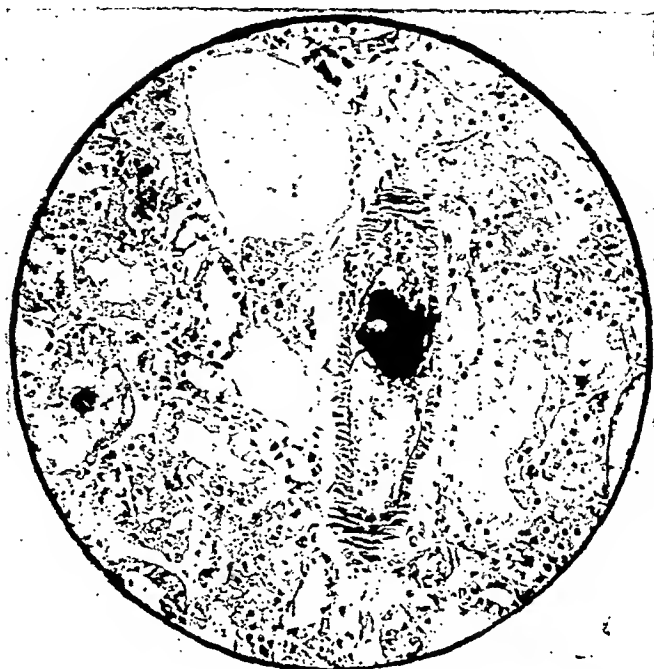


Fig. 2.—Calcified embolus in a small renal vessel (photomicrograph by A. V. Cobbett).

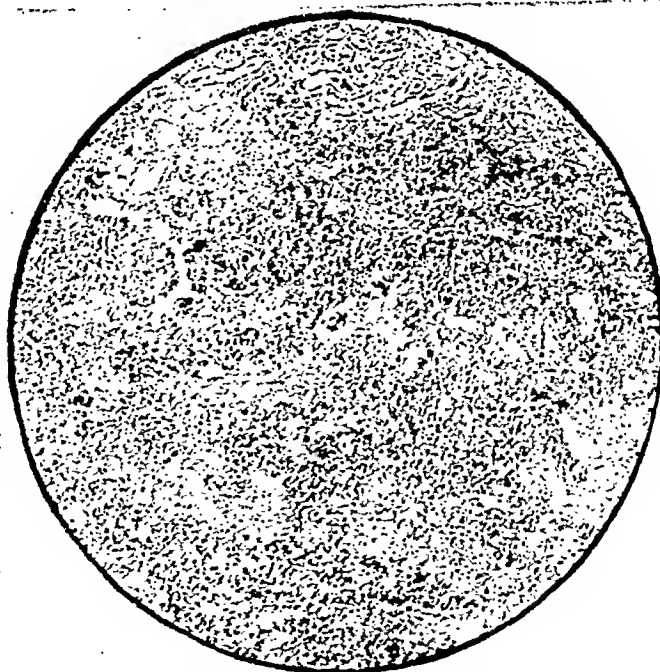


Fig. 3.—Hemorrhage in neighboring kidney substance (photomicrograph by A. V. Cobbett).

It seems probable that the hemorrhages have been caused by the sharp calcareous emboli tearing and damaging the near-by arterioles and capillaries of the kidney.

We thank Professor Fraser for permission to publish this case.

ANGINA PECTORIS IN A YOUNG ADULT*

HORACE MARSHALL KORNS, M.D.

IOWA CITY, IOWA

THE recorded incidence of Heberden's angina pectoris in children and young adults is so low that it would seem desirable to have reports of additional cases. White and Mudd,¹ who reviewed the subject in 1927, were able to collect from the literature only forty-two authenticated cases of angina pectoris in persons less than thirty years of age; to these they added eight cases of their own. Stolkind's paper,² which appeared almost simultaneously, listed twenty-nine cases, including four which he himself had observed and several which had apparently escaped the attention of White and Mudd. Since that time there have been only two additional reports (Dotti,³ Levin⁴). It is likely, therefore, that the comprehensive total of cases does not exceed sixty-five or seventy. The cases of paroxysmal cardiac pain reported by Schwartz,⁵ as he himself points out, present certain features which are irreconcilable with Heberden's angina pectoris as it is generally conceived.

REPORT OF CASE

History.—The patient, a woman, was born in 1902, and except for a great deal of tonsillitis, which was not diminished in frequency or severity by a "tonsil clipping" operation in 1909, was an unusually healthy child. In 1917 she was seized with severe tonsillitis, followed immediately by acute rheumatic fever, characterized by migratory synovitis and pain over the heart. Within three weeks her physician detected endocardial involvement and cardiac arrhythmia. The high fever began to decline after six weeks; and two months after the onset, although the patient had a rapid heart rate and slight air hunger, she was allowed to sit up in bed. A few weeks later she began to experience chilly sensations, and became once more acutely ill with high fever, rapid pulse and respiration, dull pain in the left chest and dry cough. She grew worse steadily, and after ten days had some sort of "sinking spell" lasting five minutes and characterized by extreme air hunger and apparent loss of consciousness. The fever continued for ten days more, falling by lysis. Coughing was continuous and very painful, and finally became productive of a moderate amount of sputum, at first blood-streaked, later purulent. Although a diagnosis of pneumonia of the left lower lobe, with "heart complications," was made, it is more than likely that acute pericarditis with effusion, and acute endocarditis, possibly with pulmonary emboli, were the actual pathological processes underlying this illness. Convalescence was very slow, lasting more than a year, but at last the patient regained much of her former vigor and returned to school. She completed her last three years of high school without further disability. During this time she was very active, but noticed nothing more than considerable shortness of breath after exertion until the last few months of her senior year, when she began to tire easily and to faint frequently.

*From the Department of Internal Medicine, State University of Iowa.

In January, 1923, the patient entered a nurses' training school. Two months later she was ill for a week with tonsillitis, high fever, cough and generalized aching. In May she went to bed with heart failure, and it was at this time that her aortic valve lesion was discovered. By the middle of July she was back on duty, had her tonsils removed, and continued without further interruption until December, when she was subjected to a severe emotional shock (attempted rape). The patient is very idealistic and of extremely sensitive temperament, and this experience precipitated her first attack of angina pectoris (at the age of twenty-one years). She said that she felt as if her chest were being crushed. The attacks of angina kept recurring, and in May, 1924, she was forced by increasing cardiac disability and angina to discontinue her training.

From June, 1924, until April, 1928, she worked intermittently as a "practical" nurse, during which period her activities were interrupted at least as often as twice a year by attacks of heart failure which necessitated many weeks in bed. In 1924 and 1925 she was free from angina pectoris for as long as six months at a time, but in 1926, 1927 and 1928 the seizures increased in frequency, as well as severity, until the intervals became as short as from one to three weeks. Badly discouraged, she twice attempted suicide, the second time by swallowing mercuric chloride in August, 1927. Following this she had albumin and casts in the urine for a time, and ever afterward an abnormally high blood pressure.

About the first of January, 1928, the patient had an upper respiratory tract infection which was followed by six months of cardiac invalidism and fever. During this illness she suffered considerably from a choking sensation, dysphagia and difficult breathing, and an abnormal pulsation made its appearance in the suprasternal notch. These manifestations led her physician to make a diagnosis of acute rheumatic aortitis. By June the patient was able to get about once more, and in August, 1928, she was admitted to the University Hospital.

Physical Examination.—The patient was an obese young woman of healthy appearance, weight was 215 lb., height 5 feet, 5 inches. There were no signs of syphilis, and aside from the cardiovascular system no objective observations worthy of record.

All of the essential physical signs of aortic regurgitation were readily demonstrable, *viz.*, pronounced hypertrophy of the left ventricle, a celer pulse of abnormally large volume, and a diastolic murmur originating at the aortic orifice. There was nothing to indicate the presence of any other valve lesion.

Enlargement of the ascending portion of the aorta was betrayed by the ready accessibility of the innominate artery in the suprasternal notch, a vigorous systolic impulse and pronounced diastolic impact over the aortic area, parasternal dullness in the second intercostal space to the right of the sternum, and an accentuated aortic second sound. The last named sign of an abnormally accessible aorta was particularly noteworthy in this case because of the partial replacement of the sound by a loud diastolic murmur.

In spite of the central leak, the minimum diastolic arterial pressure tended toward a normal, or slightly increased, level. An average of fifteen measurements made under widely varying conditions was 81 mm. Hg. Only twice was it found to be below 70 even when measured immediately after the administration of amyl nitrite. The highest figure recorded was 100, the lowest, 60. Similarly, the average maximum systolic pressure of 185 mm. Hg. was more than commensurate with the intrinsic demands of the patient's aortic regurgitation. These facts were taken to indicate an increase of arteriolar resistance, a factor which may well have contributed to the angina pectoris.

There was little evidence of stasis proximal to either ventricle. Most of the 35 per cent reduction of vital capacity could be explained by obesity, and the lungs were free of moisture. Slight edema of the ankles occurred from time to time, but engorgement of the liver or veins of the neck was never demonstrable.

Laboratory Examination.—An electrocardiogram showed normal cardiac mechanism, preponderance of the levoecardiogram, and, in Lead III, an iso-electric P-wave, a slightly inverted T-wave, and slurring of QRS. The blood Wassermann reaction was negative. Renal resourcefulness, as measured by the usual methods, was undiminished. The urine and blood were normal. Teleroentgenograms succeeded in giving an indication of the left ventricular hypertrophy, and were reported also as showing "accentuation of the aortic knuckle."

Summary.—History of repeated tonsillar infections, rheumatic fever, pancarditis, aortitis, myocardial failure, angina pectoris, poisoning by mercuric chloride. Presence of left ventricular hypertrophy, celer pulse of large volume, aortic diastolic murmur, signs of an abnormally accessible ascending aorta, elevation of arterial blood pressure. No signs of nephritis, no clinical or serological indications of syphilis.

Diagnoses.—Aortic regurgitation of rheumatic origin; rheumatic aortitis; angina pectoris (Heberden); arteriolar hypertonus.

Subsequent Course.—After a prolonged period of observation, covering many attacks, all who saw the patient became convinced that she suffered from genuine angina pectoris. The seizures were precipitated by exertion, excitement, or exposure to heat or cold, and were always accompanied by severe *angor animi*. The pain began in the precordia or left side of the neck, and radiated up the neck, down the left arm, and throughout the whole left chest. The blood pressure did not rise appreciably. Nitrites always gave prompt relief. The number of paroxysms was reduced considerably by continuous administration of moderate doses of euphyllin and tincture of digitalis.

A year later (August, 1929) the patient was re-examined and her condition found to be essentially unchanged. She had reduced her weight to 165 lb. The intervals between anginal seizures were averaging three or four weeks in length. The electrocardiogram remained as before.

In October, 1930, the patient's weight was about 155 lb., and she was somewhat more active. The maximum inter-anginal interval was six weeks. Digitalis and euphyllin continued to be absolutely essential to her comfort.

COMMENT

This case illustrates again the old observation, recently re-emphasized by White and Mudd, that Heberden's angina pectoris in young persons seems to be related definitely to rheumatic aortic regurgitation. In addition, in presenting more than merely inferential evidence of rheumatic aortitis, it calls particular attention to the possibility that rheumatic infection of the root of the aorta plays an important etiological rôle in the angina pectoris of the young.

REFERENCES

1. White and Mudd: Angina Pectoris in Young People, *AM. HEART J.* 3: 1, 1927.
2. Stolkind: Angina Pectoris in Children: Notes on Cases and Pathogenesis, *Brit. J. Child. Dis.* 25: 1, 1928.
3. Dotti: Intorno a un caso di sindrome anginosa in un ragazzo; sua frequenza nell'infanzia e nell'adolescenza, *Riv. di clin. pediat.* 26: 350, 1928.
4. Levin: Angina Pectoris in a Child, *AM. HEART J.* 3: 495, 1928.
5. Schwartz: Paroxysmal Cardiac Pain, the Syndrome in Young Adults With Rheumatic Valvular Heart Disease, *AM. HEART J.* 2: 497, 1927.

SURGICAL ARTERIOVENOUS ANEURYSM IN THE TREATMENT OF THORACIC ANEURYSM

A CASE REPORT

JOSEPH UTTAL, M.D.
HEMPSTEAD, N. Y.

IN 1926 Babcock¹ presented a patient upon whom he operated for the cure of a thoracic aneurysm. The operation was based upon the principle that by increasing the velocity of blood passing through the aneurysmal sac, the intravascular tension will be diminished. This was attained by making an end-to-end anastomosis between the common carotid artery and the internal jugular vein. In effect, the operation produces a large leak from the aneurysm back to the right heart.

This is in accord with the simple hydrodynamic law that a liquid moving through a tube under pressure exerts pressure against the wall of the tube inversely as the velocity of flow through the tube. A reduction of resistance causes an increase in the velocity of the blood through the sac, resulting in a reduction of the lateral pressure on the walls of the aneurysm, thereby lessening the tendency of the aneurysm to burst.

The patient that he operated upon was in a sufficiently precarious condition to warrant the employment of such a radical procedure. After a stormy postoperative course the patient rapidly improved and was able to return to work.

X-ray studies showed a definite decrease in the size of the aneurysm and a slight increase in the size of the heart.

At Mount Sinai Hospital a similar patient presented himself in imminent danger of rupture and death. The same operation was considered, but it was felt that the patient was too poor a surgical risk. It was decided to perform a side-to-side anastomosis between the brachial artery and vein in an attempt to reduce the intra-aneurysmal pressure. A study of the case will show that the result of the operation was not in accord with expectations.

In 1923 Lewis and Drury² showed clinically in five cases of arteriovenous aneurysm resulting from war injuries and experimentally after operations on dogs that arteriovenous aneurysm or side-to-side anastomosis resulted in a lowering of the diastolic pressure, a water-hammer pulse with a collapsing quality, an increase in the blood pressure in the leg (Hall and Rowland sign of differential blood pressures in the arm and leg), capillary pulsation, increased heart rate, and enlargement of the heart; these signs in other words represented the hydrodynamic phenomena of aortic regurgitation. Gage and Herrmann³ confirmed these observations.

CASE REPORT

J. M. P., aged fifty-two years, seaman-painter, was admitted to the Mount Sinai Hospital, New York, on April 10, 1928, complaining of a painful lump of two months' duration on the anterior chest wall. He had been married for eight years, and his wife had never been pregnant. He admitted having had a chancre on the penis twenty years before, and had received local and general treatment at that time. He had been subject to pains in the anterior chest radiating to the right scapula and arm for two years. The pains were intermittent and lasted only from three to five days at a time. They had decreased in severity until two months before admission, when he had a sudden severe pain in the same location; the pain disappeared as suddenly. In twenty-four hours he noticed a lump protruding from the anterior chest wall. Since then the pain had been less, but the mass had increased in size. The mass showed pulsation, which increased in intensity, and lately increased pain was noted.

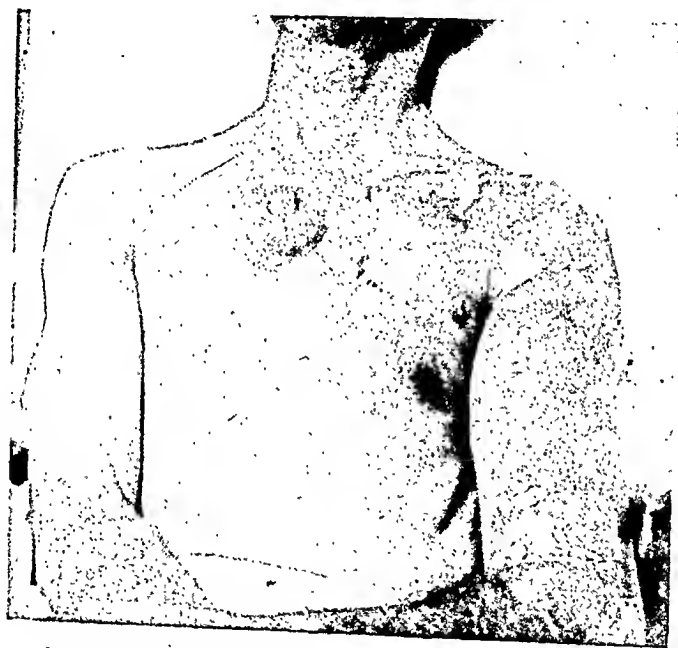


Fig. 1.—Photograph showing the aneurysm on the anterior chest wall and the swelling of the left arm two weeks after operation.

The physical examination revealed irregular, unequal pupils, which did not react to light; an expansile mass on the anterior chest wall, 8 cm. in diameter and 4 cm. in height, just to the right of the sternum. The heart was enlarged to the left and downward, and the mediastinal dullness was widened on percussion. At the apex the sounds were distinct and there was a systolic murmur. At the aortic area the second sound was present and there was no diastolic murmur. Over the aneurysm there was a low pitched systolic and diastolic bruit. The systolic bruit was transmitted to the vessels of the neck. There were no signs of aortic insufficiency. The fundi were normal. The blood Wassermann test was four plus. The urinalysis was normal, and the blood count showed hemoglobin of 80 per cent, white blood cells 10,500 per cmm., polymorphonuclears 49 per cent, eosinophiles 1 per cent, lymphocytes 48 per cent, and mononuclears 2 per cent.

Within two weeks the mass had increased in size and measured 10.5 cm. in diameter and 5.5 cm. in height. Direct arteriovenous anastomosis between the common carotid artery and the internal jugular vein on the right side was considered but dismissed in favor of the side-to-side anastomosis between the left

brachial artery and vein. This was done in the usual method by Dr. Edwin Beer. When the operation was completed, the vein gradually dilated under observation and the radial pulse remained palpable. The superficial veins distal to the anastomosis became dilated and remained engorged. The blood pressure taken in the leg dropped from 120/60 mm. before operation to 120/30 mm. after operation. In the arm the blood pressure dropped from 145/95 mm. to 120/55 mm. These readings were taken at different times.

The immediate postoperative result was freedom from pain. The veins in the antecubital fossa became more distended. The aneurysmal mass appeared to increase in size. Two weeks after the operation, the patient began to complain of pain at the site of the operation, where there appeared an area of brawny indura-



Fig. 2.—Teleroentgenogram of chest.

tion. This extended down the left arm, and remained for one week. The radial pulses were equal, and the bruit over the site of the anastomosis persisted. Wet dressings were used in the treatment of this condition, which was probably due either to a phlebitis or to mechanical obstruction to the return flow of the blood.

The electrocardiographic tracing before operation showed a slight thickening of the QRS complex in Lead III, but no other abnormality. After operation, no abnormality was found.

The teleroentgenogram showed a saccular aneurysm involving the ascending arch of the aorta, and four weeks after the operation a slight increase in the size of the aneurysm was noted.

The patient was discharged apparently improved but returned in ten days with the mass somewhat larger protruding from the anterior chest wall. The superficial

skin was ulcerated, and bright red blood was oozing from the eroded areas. The next morning the patient suddenly began to bleed profusely, became exsanguinated and died.

The post-mortem report revealed that beneath the defect in the skin and sternum as well as the second left costal cartilage, lay the aneurysm occupying the first portion of the aorta, with a perforation, 2 cm. in diameter, covered by a blood clot. There was a second smaller aneurysm to the right of the first. There were also present a luetic aortitis and an acute splenic tumor. The anastomosis between the left brachial artery and vein was patent.

BLOOD PRESSURES BEFORE OPERATION

| DATE | LEFT | RIGHT |
|--------------------------------|--------------|------------------------------|
| April 10, 1928 | 140/80 | 135/75 |
| 19, | | 140/90 |
| 22, | | 145/95 |
| 10 P.M. | 120/60 (leg) | |
| AFTER OPERATION—APRIL 22, 1928 | | |
| 11 P.M. | 120/32 | |
| 12 Noon | 110/30 | |
| 23, | 120/60 | 115/55 |
| 24, | | 120/60 |
| 26, | | 106/58 |
| 27, | | 116/60 |
| 29, | 102/48 | 104/50 |
| 30, | 116/65 | 116/60 |
| June 13, | 126/72 | 118/68 before exsanguination |

COMMENT

In the case reported the operation performed served to add the further embarrassment of the hydrodynamics of an aortic insufficiency to a circulation already embarrassed by an aneurysm.

The Babcock operation has possible merit in that it is based on a sound hydrodynamic principle. The hydraulic effect of an end-to-end union is entirely different from that of a side-to-side communication in the treatment of thoracic aneurysm. This is borne out clinically in the case presented.

It is obvious that no hard and fast conclusions can be drawn from the report of this case, except that the formation of an arteriovenous aneurysm to relieve the lateral pressure on the walls of a thoracic aneurysm was of no avail.

This case report is presented through the courtesy of Dr. George Baehr of the Second Medical Service and Dr. Edwin Beer of the Second Surgical Service of the Mount Sinai Hospital of New York.

REFERENCES

1. Babcock, W. W.: A New Treatment for Thoracic Aneurysm, *Ann. Clin. Med.* 4: 933, 1926.
2. Lewis and Drury: Observations Relating to Arteriovenous Aneurysm, *Heart* 10: 301, 365, 1923.
3. Gage and Herrmann: Observations on Experimental Arteriovenous Aneurysm. Cardiac Hypertrophy in Arteriovenous Aneurysm. *Proc. Soc. Exper. Biol. & Med.* 25: 765, 1928.

Department of Reviews and Abstracts

Selected Abstracts

Levine, Samuel A., Andren, Thekla, and Homans, Katharine A.: Nosebleed and Vomiting in Rheumatic Individuals. *New England J. Med.* 203: 832, 1930.

The frequency of spells of nausea, vomiting, and epistaxis was ascertained in one hundred individuals suffering from rheumatic fever or one of its allied conditions like chorea or rheumatic heart disease. This was compared with the frequency with similar symptoms in a control group of one hundred nonrheumatic individuals of approximately the same age coming to a surgical clinic. According to the method used in estimating the occurrence of these symptoms they were found to be three to four times as frequent in the rheumatic as in the non-rheumatic group. The authors believe that attacks of inexplicable nausea and vomiting and spontaneous nosebleed are in some way related to the rheumatic infection. They occur frequently during a period of the infection that generally is regarded as inactive. Epistaxis particularly may occur for years preceding the first definite attack of rheumatism. These features, together with others more commonly emphasized, will enable the physician to identify as rheumatic many conditions which at present go unrecognized or misdiagnosed.

Shoemaker, Robert, III, and Eckels, John C.: Bullet in the Heart. *New England J. Med.* 203: 195, 1930.

A white woman twenty-three years old was brought into the hospital with two bullet wounds in her chest. One bullet was found localized in the chest wall and under local anesthesia a 22-caliber bullet was removed in the situation indicated by the x-ray report. The other bullet was localized apparently in the wall of the ventricle on the anterior surface probably in the right side. It showed an excursion of 2 cm. during the cardiac cycle. It was decided that since the patient was recovering after emergency shock treatment that no attempt should be made to remove this foreign body. Physical examination otherwise was unimportant. Electrocardiograms made during convalescence showed a normal cardiac rhythm. The patient recovered, was discharged at four- and eight-week intervals for reexamination.

Fitzhugh, Greene: A Clinical and Pathological Study of Chronic Myocarditis. *New England J. Med.* 203: 201, 1930.

An analysis of the clinical and pathological records of 228 selected fatal cases was undertaken to study the relation between the clinical syndrome and the necropsy findings in cases of cardiac failure. Cases chosen for study were those in which the heart showed at necropsy hypertrophy and dilatation, fibrosis, or infarction of the myocardium. Hearts with valvular lesions were not included. All of these except 28 showed during life clinical evidences of myocardial insufficiency. Of the 228 cases, 125 died of cardiac failure and form the cardiac group. Fifty-five died of nephritis, 14 of cerebral hemorrhage, and 34 of miscellaneous causes, making up the noncardiac group. The author then proceeds to analyze the various an-

atomical lesions found at necropsy and also the usual symptoms shown during life in these two groups of patients. Importance of such studies as this cannot be overemphasized in throwing light on the significance of various clinical symptoms.

Hoskin, Jenner: The Effect of Auricular Fibrillation on the Operative Risk in Hyperthyroidism. *Brit. M. J.* July 26, p. 138, 1930.

The present paper is the result of an investigation of 356 consecutive cases of Graves' disease, exophthalmic and toxic, in which all but 4 had operative treatment; 315 were cases of exophthalmic goiter and 41 of toxic goiter. Thirty cases of auricular fibrillation were found, 22 among the exophthalmic goiter cases and 8 among the toxic, a total of 9.52 per cent. It is probable that a few cases of transient fibrillation may have been overlooked.

There were 12 transient cases, of which 10 occurred after partial thyroidectomy; in the remainder, paroxysmal attacks of auricular fibrillation were noted electrocardiographically prior to operative treatment. In all 12 cases normal rhythm was reestablished within a week of the operation without quinidine being administered. Of the 18 cases of permanent fibrillation, there were 4 deaths, 3 following operation. Of the remaining 14 cases, 7 became normal within a few days of operation, and in 7 the irregularity persisted. Of these 7, three were not operated upon, 3 had partial thyroidectomy performed, and in 1 case the superior thyroid vessels were tied. One of these cases in which normal rhythm was restored by partial thyroidectomy relapsed into auricular fibrillation four months later.

Out of the 356 cases investigated, the total mortality was 20. The presence of auricular fibrillation must be regarded as a distinctly unfavorable complication during operation. It is associated with cardiac enlargement, rapid pulse rate, and signs of congestive failure. The effect of the toxic thyroid secretion as shown by the raised basal metabolic rate is aggravated by an added impairment of cardiac function caused by the congestive failure. It is essential, therefore, that the thyrotoxicosis should be reduced and the ventricular rate controlled before operative procedure is contemplated. Lugol's solution in combination with digitalis is indicated in preparing these patients for operation.

Willner, Otto: Some Observations on Mitral Stenosis and Measurements of Normals Among Chinese. *Am. J. M. Sc.* 180: 200, 1930.

Among 24,000 patients admitted to the Peiping Union Medical College Hospital during seven and one-half years, 95 men and 62 women were found to have mitral stenosis as a single or combined valvular lesion. It would seem that there is a low incidence of typical rheumatic fever among these people. In this group of patients it was found that the asthenic habitus was prevalent.

For comparison an examination was made of 150 healthy young Chinese adults in order to determine whether there was a correlation between the 3 predominating characteristics found in the group of individuals with mitral stenosis, namely, asthenic build, mitral configuration of the heart, and a large angle of the electrical axis. It was not clear that such a correlation existed.

Parsonnet, Aaron E., and Hyman, Albert S.: Barium Chlorid in the Stokes-Adams Syndrome of Complete Heart-Block: Negative Results in Eight Cases. *Am. J. M. Sc.*, 180: 356, 1930.

The authors have been interested in the use of barium in a series of eight cases of complete heart-block complicated by the Stokes-Adams syndrome. In none of these cases were they able to obtain any semblance of pharmacological or physiological action either good or bad. Special attention was focused upon the quality and the source of barium employed. Amounts varying from 0.04 to as much as

0.6 gram were given in twenty-four hours; these doses were continued in various cases from one week to three months, and electrocardiographic control of each case was made from every two weeks to two months. While this series of eight cases is not large, the authors point out that the Stokes-Adams syndrome is by no means common and that the series is extensive enough to challenge the test of barium efficacy.

Harvey, Earle A., and Levine, Samuel A.: A Study of Uninfected Mural Thrombi of the Heart. Am. J. M. Sc. 180: 365, 1930.

A study was made of all the necropsy protocols at the Peter Bent Brigham Hospital for the interval 1913-1929 in which 2,091 records were reviewed. The incidence of thrombi of the heart in patients coming to necropsy was found to be approximately 5.3 per cent or 111 instances. Seventy-three occurred in males and 38 in females. The thrombi were noted most frequently in the later years of life. The two decades from fifty to sixty-nine included more than half of all the cases. A positive Wassermann was noted in about 10 per cent, which is about the average incidence in all cases coming to the hospital. The frequency of sites of formation of single thrombi were: left ventricle 31, right auricle 28, left auricle 6, right ventricle 4. There were 42 cases of multiple thrombosis. The apices of the ventricles and auricle appendages were the most frequent sites of formation of mural thrombi. Auricular fibrillation definitely increases the incidence of auricular thrombosis.

The authors believe from their study that the two most frequent mechanisms for the formation of cardiac mural thrombi are the myocardial degeneration associated with coronary arterial disease and the improper functioning of the auricles leading to blood stasis. The diagnosis of cardiac mural thrombi rarely is made during life but should be suspected in cases of coronary thrombosis and coronary valvular disease showing evidence of emboli.

Niles, Walter L., and Wyckoff, John: Studies Concerning Digitalis Therapy in Lobar Pneumonia. Am. J. M. Sc. 180: 348, 1930.

This study is an attempt to determine the effect of digitalis as a therapeutic measure in the care of patients with lobar pneumonia. The number of cases available for the study has been sufficiently large to warrant drawing conclusions of value. The study has been conducted over a period of at least two years' time on patients admitted to the hospital with lobar pneumonia under carefully controlled conditions and given digitalis in sufficient amounts to produce clinical effects. Results of this study should be known to every clinician, since it marks a most important contribution to the subject.

It would seem that patients with pneumonia are not benefited by digitalis therapy; in fact, in this series of cases the mortality was slightly higher in the group of patients who were digitalized than in those who received none.

Numerous tables analyze results from several standpoints. From a study of the tables it would seem that for every one hundred cases in the control group who died there were one hundred and twenty-two fatalities in the digitalis treated group. In a small group of patients receiving a preparation of digitalis with higher potency than indicated the mortality was 13.5 per cent higher than of the control group, or at the rate of 140 patients for every 100 control patients. The mortality rate is higher for both sexes in the digitalis treated groups as compared with that of the controls. Tables also show that the mortality of the digitalis treated cases is higher than that of the corresponding controls in both the older and younger groups. It is also shown that in all types of pneumonia, except type

II, the mortality of the digitalis treated cases is higher than that of their controls. The only exception to this is that the higher mortality in the digitalis treated cases is found in the younger age group with type II pneumococcus infection. No explanation has been found for this exception. Possibly the factor of virulence in producing septic complications may determine it. The last table shows that the incidence of auricular fibrillation and auricular flutter is the same in the control and the digitalis treated group. The mortality is, however, distinctly higher in the digitalis treated group.

In conclusion, the Committee prefers to continue this investigation on the results of digitalis therapy in pneumonia and to observe a larger number of cases over a series of years. It was the unanimous opinion of the Committee and its advisers that the results obtained thus far do not justify continuing the routine administration of digitalis to patients suffering with lobar pneumonia.

King, Frances W., and Hansen, Olga S.: Electrocardiographic and Roentgenographic Studies of the Heart in Tuberculosis. Am. Rev. Tuberc. 22: 310, 1930.

Studies of electrocardiograms and x-ray plates have been made on one hundred unselected cases of tuberculosis at Glen Lake Sanatorium. The diameter of the heart was found to be lower in this series than in normal individuals. The hearts of one hundred cases without hypertension or heart disease coming to autopsy showed that the weight of the heart in this series is on the whole lower than that in the nontuberculous. Nearly one-third of this group had a cardiothoracic index below 40 per cent as compared with one-fifth in the normal.

The electrocardiograms of this group of patients following collapse therapy revealed that a high percentage (60 per cent) showed low voltage in one or more leads, the amplitude of the ventricular complex measuring not more than 5 mm. Roentgen ray studies indicated that the heart shadow was displaced by tuberculous processes in a considerable number of cases. Study of electrocardiograms in these cases with displacement of the heart shadow yields insignificant results. The incidence of low voltage is practically the same in the right-sided heart and in the normally placed heart. The infrequent occurrence of low voltage in Lead I in the presence of left heart displacement is the only point worthy of note in these figures.

Hansen, Olga S., and King, Frances W.: The Influence of Pulmonary Collapse on the Electrocardiogram. Am. Rev. Tuberc. 22: 320, 1930.

Electrocardiograms have been studied in sixty-six patients who have undergone seventy-three pulmonary collapse procedures, analyzing findings before and after collapse. These procedures are almost invariably followed by changes in amplitude of the electrocardiographic waves, R-wave modification occurring in 96 per cent of the cases, but the type and the degree of variation are not constant or predictable, according to either the side involved or the procedure carried on.

Evidence suggests that the changes are due to changes in heart position, influenced largely by pleural and mediastinal adhesions, more than by myocardial factors.

Hitchcock, C. H., McEwen, Currier, and Swift, Homer F.: Antistreptococcus Serum Treatment of Patients with Rheumatic Fever. Am. J. M. Sc. 180: 497, 1930.

The authors have observed the therapeutic effects of antistreptococcus serum on a group of patients in the hospital for the Rockefeller Institute with rheumatic fever. Three types of serum were used: (1) an antihemolytic streptococcus serum; (2) SCA (indifferent streptococcus) serum, both bovine and equine, and (3) an

anti-green streptococcus serum. The reactions following the use of any one of these three types of serum were irregular and while at times severe, were generally mild and produced no injury to the patient. No well-defined improvements could be observed following the use of sera.

The authors point out that it is not to be expected that any marked specific beneficial action would follow antistreptococcus serum therapy in rheumatic fever, for the disease is not of the general type which would respond favorably to a serum. It is not an acute disease like diphtheria, tetanus or scarlet fever but a subacute or chronic infection resembling tuberculosis or syphilis in many of its features. The amount of material responsible for the various manifestations of the disease which are elaborated and conveyed to the blood varies in amount and intensity over long periods of time.

The authors conclude that antistreptococcus serum in no way should replace the long established therapy of rheumatic fever and that it does not apparently add enough to warrant its universal adoption. In their experiments the unpleasant reactions sometimes attendant upon its application have not been outbalanced by a reciprocal certainty of therapeutic benefit.

Leech, Clifton B.: Streptococcus Viridans Endocarditis in Children. *Am. J. M. Sc.* 180: 621, 1930.

The records of the Harriet Lane Home revealed 13 instances of streptococcus viridans endocarditis proved by blood culture or by autopsy, 2 unproved but highly probable cases and 1 streptococcus viridans septiceemia without endocarditis. The 15 cases represent an incidence of approximately 0.1 per cent. An analysis of these records is partially indicated in the accompanying table. A discussion of the symptoms and signs indicates that this infection produces a clear clinical picture of sufficiently constant characteristics to permit diagnosis even without culture of the blood.

Fishberg, Arthur M.: Auricular Fibrillation and Flutter in Metastatic Growths of the Right Auricle. *Am. J. M. Sc.* 180: 629, 1, 1930.

Three cases are described in which secondary malignant growths in the right auricle were accompanied by auricular fibrillation or flutter. In the first of these cases the involvement of the right auricle by the tumor was suspected during life; in the two succeeding cases this diagnosis was considered very probable.

Sheldon, Wilfrid: Rheumatism in Childhood. *Lancet* 11: 394, 1930.

This paper is based on the notes of six hundred consecutive cases of rheumatism seen during the last two years at the Rheumatic Clinic of the Hospital for Sick Children, Great Ormond Street. The children were divided into the following four groups.

One group was of 235 children with rheumatic pains in the limbs. These children form an important group, because of the possibility of a later development of heart disease. The pains rarely develop before the age of three years. They are especially frequent during the night, and they occur in many parts of the body, chiefly the legs. An accompanying curve shows that the pains occur more frequently during the seasons when there is greater rainfall. Fifty-two of 266 children with rheumatic heart disease complained of these pains as the only symptoms preceding the discovery of the heart disease; similarly 15 children out of 197 cases of chorea gave a history of such pains in the limbs.

The second group was of 133 children with a history of rheumatic fever or acute articular rheumatism. These children are rarely seen before the age of three years. The author describes the well-known characteristics of rheumatic fever in young children. He believes that the relationship between rheumatic fever and heart disease is well recognized. In this group, 93 children (70 per cent) showed evidence afterward of cardiac involvement; of the remainder, the rheumatic fever was followed by chorea in 5 cases. Only 23 children had been entirely free of rheumatic symptoms since their attack of rheumatic fever.

The third group was of 197 children with chorea. Of this group, rheumatic heart disease occurred in 52; rheumatic fever preceded the chorea in 5 cases, and in 15 instances rheumatic pains in the limbs either accompanied or followed the chorea. Children with chorea are apt to be quick and intelligent and keen on their school work.

The fourth group was of 266 children with rheumatic heart disease, a percentage of 44. The author discusses the early diagnosis of the heart disease, particularly the differentiation of murmurs associated with organic valvular lesions and functional disturbances. Aortic regurgitation was present in 6 per cent of this group of children.

The question of tonsillectomy in children with rheumatism is discussed briefly. In this group of children tonsillectomy has been performed on 90 per cent. Three hundred ninety-three were operated on before admission to the clinic. Cases in which visible tonsil remnant remained after the operation have not been included in this study. Approximately one-third of the cases of rheumatic pains, chorea, and rheumatic fever begin these symptoms of rheumatic infection after the tonsils have been removed. The author believes that unless it can be shown that tonsillectomy has a definite influence in the prevention of cardiac disease there seems small justification for the operation merely on the ground that the child is a rheumatic suspect. It seems more probable that the value of tonsillectomy in rheumatic children is in proportion to the degree of impairment of the general health attributable to the tonsils.

Buffum, William P.: Management of Convalescence in Rheumatic Heart Disease. Rhode Island M. J. 13: 127, 1930.

The author discusses the many criteria that can be used in watching individuals convalescent from active rheumatic fever and heart disease. Usual points to be noted are the temperature, pulse rate, general appearance, and color of the child, weight curve, and the physical signs noted on examination of the heart. Furthermore, subcutaneous nodules should be looked for; the leucocyte count should be followed, and occasionally the determination of vital capacity may serve as a guide to satisfactory progress. The vital capacity can be used as an index of the functional capacity of the heart.

He points out that the determination of whether or not the active disease has ceased is at times very difficult and that it is not possible to rely entirely on any one of the above signs. During further convalescence, after the patient is up, any recurrence of these signs of active disease shows that the patient should be put to bed again.

The author makes the important statement that in general it is better to consider the child as a whole rather than to focus the attention too much on the heart. He discusses the regulation of exercise and the general care that should be provided these patients. He also discusses the value of tonsillectomy in the control of further attacks of rheumatic fever.

Smith, Arthur L.: Configuration of the Heart in Cardiac Disease. Neb. State M. J. 15: 337, 1930.

The author points out that accurate diagnosis of heart disease depends upon careful history taking, complete physical examination, and laboratory findings combined with employment of sensitive scientific instruments and exacting interpretation of the findings. No one method will suffice for an accurate diagnosis.

He believes that there is no such thing as x-ray diagnosis of heart disease. The size, shape, and position of the heart vary greatly in a normal person, and if these alone are considered, the diagnosis will often be incorrect. He describes the usual appearance of the heart in roentgen ray films and also describes the changes that occur as the result of valvular disease and muscle enlargement. He believes that each condition affects the appearance of the heart picture in a characteristic way.

Drake, Carl B.: The Clinical Aspects of Sclerotic Changes in the Aortic Valve. Minn. Med. 13: 628, 1930.

Four cases are reported in which there was thickening with calcification in the aortic valves with physical signs suggestive of aortic stenosis. The author points out that the lesions may arise in old healed rheumatic valvular endocarditis. He believes that the aortic stenosis is the predominating lesion produced by the sclerosis but that there may be in many instances also an accompanying aortic insufficiency. Physical signs of aortic insufficiency may be obscured by those of the stenosis.

The sclerotic process producing aortic stenosis does not particularly shorten life, is a gradually progressive affair, and the patient usually adapts himself to a definite limitation in the field of his cardiac response.

McKinlay, C. A.: Valvular Heart Disease in Young Adults. Minn. Med. 13: 624, 1930.

The observations noted in this paper are from 67 cases, chiefly university students who were found on entrance and subsequent physical examination to have valvular heart defects. They represent a selected group without cardiac decompensation who had suffered little or no inconvenience from their condition.

A relatively high incidence of aortic insufficiency was noted in the series. Clean tonsillectomy had been done in only about one-half of the cases. Frequency of hypertrophic and follicular pharyngitis is discussed in view of possible significance in relation to rheumatic fever, the methods of treatment and prevention.

Jolliffe, Norman: Liver Function in Congestive Heart Failure. J. Clin. Investigation 8: 419, 1930.

The frequency of clinical jaundice in a series of 231 patients with congestive heart failure was observed to be 2.1 per cent. The jaundice in this type of failure may be of either the obstructive or the nonobstructive type. Using various methods to study liver function, 15 of the 16 patients had some alteration in liver function, though no characteristic type was found. Three subjects showed only one abnormal response to liver function tests; only one subject showed all tests abnormal.

No parallelism between degree of heart failure and impairment of liver function could be noted in individual cases. As a group there was perhaps a parallel between the changes in liver function and the degree of edema and size of the liver. Any liver dysfunction induced by an attack of chronic passive congestion is apparently not permanent. Liver dysfunction still in evidence after recovery from an attack of chronic passive congestion indicates an independent liver impairment.

Boek, A. V., Dill, D. B., and Edwards, H. T.: On the Relation of Changes in Blood Velocity and Volume Flow of Blood to Change of Posture. *J. Clin. Investigation* 8: 533, 1930.

Estimations of the circulation time as measured by reaction to histamine indicate a retardation of the velocity of blood flow in the standing position in man. The authors believe this fact supports previous experimental evidence showing a reduction of the total output of the heart when the subject stands still.

Pardee, Harold E. B.: The Significance of an Electrocardiogram with a Large Q-wave in Lead III. *Arch. Int. Med.* 46: 470, 1930.

Attention is directed to the occurrence of records showing left axis deviation of QRS or a normal electrical axis, combined with a large Q-wave in Lead III, one that is 25 per cent or more of the largest deflection of QRS in whichever lead this may occur.

The majority of such records are obtained from patients with the aural syndrome, but certain patients with myocardial fibrosis and congestive failure, certain patients with rheumatic heart disease, especially with pericarditis, and a few with hypertension will give such records. Certain patients who have cardiac symptoms but no definite evidence of cardiac disease have been found to show this large Q-III, and rarely (twice in 277 cases) such records are obtained from apparently normal hearts.

These records show a clockwise rotation of the vectors of the QRS group, and frequently there is an inversion of T-III or of T-II and T-III. Both of these features depend on right ventricular activity, and it is suggested that the finding of a large Q-III indicates disease of the left ventricle, so that the right ventricle predominates during the spreading of the contraction in spite of the left axis deviation or normal axis direction of QRS. The effect of diaphragmatic movements on the large Q-III is noted and it is suggested that the occasional finding of a large Q-III in normal hearts may be due to an unusual distribution of the branches of the A-V bundle and that a high position of the diaphragm may be a contributory factor.

Nyiri, William, and DuBois, Louis: Experimental Studies on Heart Tonics. IV. The Main Factors of Digitalis Standardization with a New Assay Method. *J. Pharmacol. & Exper. Therap.* 40: 373, 1930.

The authors believe that warm-blooded animals are to be preferred as test material to animals lower in the animal scale and to plants. They also believe that the best way of administering heart tonics in the assay is the intravenous injection. Intravenous anesthesia is also to be preferred to the former methods of narcosis in animal experimentation in general and for the standardization of heart tonics in particular.

The fall of blood pressure to zero, approaches closest the theoretically expected end point of the experiment and thus is to be preferred to the observation of the stoppage of the heart and the general death of the animal.

Based on the study of these principal factors a practical method of digitalis standardization is described using the rabbit as test animal. This method has the following advantages: the animal is always easily available. The end point of the assay obtained by means of the drop of the blood pressure, supplementing the test of the use of ouabain, is definite and as close to the theoretical end point as may be expected. Because of the higher resistance to digitalis the method allows the testing of drugs of high concentration as well as drugs of great dilution without preliminary injurious manipulations of the heart tonics.

All methods of standardization of heart tonics, including the one herein described, are toxicity tests and use the death of the heart or of the entire organism as final criterion. In view of the therapeutic purpose of the heart tonics any method dealing with the determination of the therapeutic efficiency instead of the fatal dose obviously would be preferable. Unfortunately, such a method is not available at present.

Dawson, M. H., and Boots, R. H.: Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis. *J. A. M. A.* 95: 1894, 1930.

The authors have found a relatively high—approximately 20 per cent—incidence of patients with subcutaneous nodules in a group of approximately 200 individuals suffering with true rheumatoid arthritis. The nodules have been observed only in cases of typical rheumatoid arthritis, and in one case of Still's disease. Three of the patients in whom the nodules occurred presented a history of a previous attack of rheumatic fever; four patients showed definite evidence of rheumatic heart involvement; in one patient the development of arthritis and the appearance of nodules appeared to bear a definite relationship to a previous attack of scarlet fever.

Nodules have been exercised from 14 patients and subjected to careful histological and bacteriological examination. The material examined showed a striking uniform and characteristic picture.

This study sustains the following conclusions: The subcutaneous nodule occurring in rheumatoid arthritis is a classic lesion of this disease. The histologic appearance of these nodules is uniform and highly characteristic. There is a striking histologic resemblance between the subcutaneous nodules occurring in rheumatic fever and those observed in rheumatoid arthritis.

Sprague, Howard B., and Graybiel, Ashton: Salyrgan as a Diuretic. Report of Sixty Cases. *New England J. Med.* 204: 154, 1931.

Sixty cases treated with salyrgan are reported. Forty-six patients had cardiac diseases with digestive failure; eight had cirrhosis of the liver; four had cancer; and one each nephrosis and ovarian cyst. Diuresis was secured in 80 per cent of the cases and in 55 per cent this diuresis exceeded twice the fluid intake. The diuretic effect may often be increased by the use of ammonium chloride or nitrate.

The authors feel that the drug is an active and safe diuretic of particular value in the treatment of congestive heart failure with edema of ascites from various causes, and of nephrosis. It should be used early in the therapy of these conditions and not reserved as a drug of last resort.

The toxic effects from Salyrgan are very rare and consist of mild renal, gastrointestinal or skin irritation.

This work supports the view that the chief effect of mercurial diuretics is directly upon the kidney.

Wolferth, Charles C., and Margolies, Alexander: The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse. *Arch. Int. Med.* 46: 1048, 1930.

A series of 7 cases with varying auriculoventricular relationships all showed inequalities of the first heart sound which could be related to the lengths of the intervals between auricular and ventricular systoles. These time relations tended to be characteristic for each case, although the degree of inequality varied and exceptionally could not be recorded.

The inequalities of sound are usually detected by auscultation and furnish a valuable clinical test of dissociated beating of the auricles and ventricles. The absence of inequality of sound does not rule out the possibility of dissociated beating. In two cases inequalities in the size of the pulse waves were recorded. When the amplitude of the waves recorded was compared with the lengths of intervals between auricular and ventricular systoles, a definite relation was revealed. In both cases the curves showed similar time relations. In one, inequalities in amplitude seemed to vary from day to day, and occasionally no differences could be recorded. In three other cases tracings of the pulse waves failed to reveal changes in the amplitude of the waves that could be related to the auriculoventricular intervals.

Simultaneous records of changes in the intensity of sound and amplitude of the pulse waves showed that comparatively loud or faint sounds may be associated with comparatively large or small pulse waves. It was, therefore, concluded that while both types of changes were dependent on phenomena resulting from auricular systole, the factors concerned were not identical.

It is suggested, by indirect evidence obtained in this study that the changes observed in the amplitude of the pulse waves are due principally to the effects of auricular systole on ventricular filling and initial tension. The provisional hypothesis is adopted that inequalities of the first heart sound observed are due principally to variation in the position of the mitral leaflets at the beginning of ventricular contraction.

The data presented indicate that in the clinical evaluation of the first heart sound as evidence of cardiac vigor, modifications dependent on the duration of the auriculoventricular interval should be discounted.

Drinker, Cecil K., and Field, Madeleine E.: Absorption From the Pericardial Cavity. J. Exper. Med. 53: 143, 1931.

The pericardium in the rabbit proved to be a singularly inert protective membrane. Simple solutions placed within the sac are held without leakage and are absorbed practically entirely by the subepicardial blood capillaries. Such solutions do not leak through the extraordinarily thin pericardial membrane into the pleural cavities even if subjected to slight pressure. When substances such as serum or graphite are injected, removal is extraordinarily slow. No evidence was obtained from the study showing the abrupt direct type of lymphatic entrance which is seen in the central tendon of the diaphragm after intraperitoneal injections. Such lymph drainage as occurs is through lymphatics in the pericardium around the base of the heart and to a slight extent along lines of fat deposition in the pericardium. The subepicardial lymphatics are entered with great difficulty from the pericardial sac, a condition favorable to exclusion of the heart from participation in pericardial infections.

Book Reviews

LA PRATIQUE MÉDICALE ILLUSTRÉE. LES ENDOCARDITES INFECTIEUSES—
DIAGNOSTIC—TRAITEMENT. Directeurs Professeur E. Sergent, R. Mig-
not, R. Turpin. Par A. Lemierre and P. M. Deschamps. Paris, 1930,
G. Doin & Cie.

This is one of the series of fasciculi on various branches of clinical medicine published under the direction of Professor Sergent in Paris. Any publication bearing the signature of Lemierre is worthy of careful study, and this volume is no exception to the rule. Some forty years ago that admirable clinician Neusser, of Vienna, sent one of his assistants to study in Paris with the observation: "The French excel in symptomatology." There are indeed no clearer clinical descriptions than those of the better French clinicians, a truth to which this brochure testifies.

In the preamble the authors observe: "From a very general point of view the infectious endocarditides present themselves to the physician under two different circumstances. On the one hand, in the course of a given infection, they may constitute a complication which should be systematically sought for because we know it to be very common under such conditions, but which remains in the background and exerts no influence on the immediate prognosis; this is the situation which is generally met with in the course of acute articular rheumatism where Bouillaud's laws should always be in one's mind. On the other hand, the endocarditic complication may overshadow the other manifestations of the disease which gives it birth: it dominates the prognosis. So it is in certain malignant rheumatisms and in the greater part of the so-called ulcero-vegetative endocarditides." They accordingly consider infectious endocarditis under two headings: (1) Rheumatic endocarditis which, anatomically, is verrucose or plastic. (2) Infective endocarditis proper, malignant or septic endocarditis dependent on infection with pyogenic organisms and characterized anatomically by ulcerative and vegetative processes.

Rheumatic endocarditis they divide into (1) *Simple rheumatic endocarditis* and (2) *Malignant septic endocarditis*.

The insidious origin and course of the ordinary rheumatic endocarditis are well described and contrasted with the clinical picture of rapidly progressive rheumatic pancarditis with early cardiac failure. The differential diagnosis between acute rheumatic pancarditis and what we call infective or bacterial endocarditis is admirably set forth. They insist, especially, on the predominance of signs of cardiac failure

in the former even if they be associated with symptoms suggesting grave pyogenic infection. They devote eight pages to the careful description of malignant rheumatic endocarditis and its distinction from bacterial endocarditis.

They then take up "the infective malignant or septic endocarditides" dependent upon infection with pyogenic organisms, describing first the acute forms in a general way before taking them up from an etiological standpoint. They point out their differences from malignant rheumatic endocarditis in the existence of a septicemia, ulcero-vegetative lesions and the frequency of embolic phenomena, and they insist, particularly, on the circumstance that the cardiac phenomena remain generally in the background. The outstanding symptoms are those of a septicemia. From a general clinical standpoint they consider cases of a typhoidal aspect with high continued fever, and the pyemic type with irregular remittent and intermittent fever. They call attention to the occasional instances in which the foci of infection are parietal and difficult to recognize clinically, and they refer to that group of cases in which the onset is sudden, with early and repeated embolisms. Finally they acknowledge that one may almost speak of a "cardiac form" with terminal thrombosis of the right side of the heart and pulmonary embolisms.

From an etiological standpoint they discuss *streptococcal*, *pneumococcal*, *gonococcal* and *staphylococcal* infections, and then mention rarer forms—endocarditis due to *typhoid bacilli*, *enterococci* (which we should include under streptococci), *colon bacilli*, *M. tetragenus* and the pneumobacillus.

On page 30 the reviewer is quoted as having found infection with pneumococcus I more frequent than with the other types. With augmented experience the reviewer has found that among 31 cases the infection has been evenly divided between Types I, II and IV, one case only showing a Type III infection.

The authors then take up *subacute, infective, malignant, endocarditis* which they distinguish from the *infectious malignant endocarditis of a prolonged course* in that its duration is from one to three months only. The description is admirable. At the outset they insist on the frequency with which the process takes its origin on the basis of an old valvular lesion, and that, after all, as Vaquez happily expressed it, "it is, in reality, a manner of death for patients the subject of valvular lesions."

On page 37, in speaking of embolic phenomena, they point out the difference between the clinical evidences of embolisms springing from thrombi in right and left heart. On the same page the remarkable statement is made that subacute endocarditis of the left heart is only observed in chronic mitral disease ("qui ne s'observe guère que chez les mitraux"). This is perhaps a little exaggerated. The reviewer

can put his hand immediately on the records of nineteen instances of infective endocarditis of the left heart of a duration of from one to three months in his own series, in which the aortic valves were involved. In eight of these the mitral valves were unaffected; in three more the mitral involvement appeared to have been coincident with that of the aortic valves, that is to say, purely subacute. In the streptococcal series where the infective focus is more commonly on the seat of a chronic rheumatic lesion there were nine instances of involvement of the aortic valves, in two of which the mitral curtains were normal; in a third, the mitral involvement appeared to have been purely subacute.

They then consider "*Infective malignant endocarditis of slow or prolonged course.*" The manner of origin and the course of the infection are carefully described and the diagnostic features judiciously discussed. Under specific headings are considered (1) the *probable* signs—fever, anemia, splenomegaly, arthralgia—in association with the relative absence of alteration in the patient's general condition and of signs of cardiac insufficiency, and then (2) the *certain* signs, especially embolic. They emphasize the circumstance that the emboli are not generally infective, at least in the sense that they do not, as a rule, result in abscesses, but produce mainly mechanical effects. This, in a general way, is true, but it is only relatively so, for one should remember the frequency with which mycotic aneurysms, etc., may follow.

The authors are, I think, a little too absolute in their unfavorable prognosis. There are undoubted recoveries, rare though they be.

Under the heading of "clinical forms" they consider those instances in which the disturbances of the patient's general condition is in the foreground; those in which the painful phenomena—arthritis, myalgic, etc.—are the most prominent features; those in which the visceral changes are notable, embolism, degenerative changes giving rise to Hippocratic fingers, nervous forms of the disease, renal forms, respiratory or more rarely, the occasional cardioplegic forms. They mention the occasional termination with an acute exacerbation of the symptoms dependent upon renal or cardiac insufficiency or upon an aggravation of the septicemia or a secondary infection. Finally they acknowledge that in some cases the valvular lesions may be primary, arising on curtains previously unaffected. They insist that the foci are frequently parietal making the diagnosis difficult. In the experience of the reviewer parietal endocarditis though common is rarely unassociated with valvular lesion.

On pages 55 and 57 there is an excellent summary of the differential diagnostic features. The authors are perhaps a trifle too dogmatic in asserting that emboli are not seen in rheumatic cardiac disease. There are, of course, instances of embolism in subacute rheumatic heart disease with thrombosis of the auricular appendages in auricular fibrilla-

tion, and the reviewer has seen repeated embolisms due to massive thrombosis on the wall of the left auricle in an instance which simulated subacute infective endocarditis to an extraordinary degree.

They justly point out that in doubtful cases, in childhood and adolescence, one should turn toward the diagnosis of rheumatic endocarditis. The reviewer is, however, inclined to believe that secondary bacterial endocarditides are commoner in childhood than is generally believed. In only 6 of 146 instances of streptococcal endocarditis of subacute or prolonged course in his series were the subjects in the first decade of life, yet the proportion of children to adults in his material was for a long time very low. Again one must remember that the cultivation of streptococci from the blood of patients with rheumatic fever is not rare, and of itself does not justify a diagnosis of vegetative or ulcerative endocarditis.

The writers wisely refer to the frequent slow growth of the nonhemolytic streptococci and advise the observation of the cultures for eight days or more. The reviewer would extend this even further. He has seen abundant growth appearing first thirteen days after the making of the cultures.

In their discussion of the *treatment of rheumatic endocarditis* the writers are sanguine as to the *preventive* value of salicylates. They devote a page and a half to the discussion of the intravenous use of salicylate of sodium in rheumatic carditis. They recognize its dangers—the sclerosing action on the veins, “salicylate shock,” and, in one instance, sudden death, but they feel that with care, this method of treatment is free from danger and is sometimes of value. They advise 10 per cent solutions of salicylate of sodium in 10 per cent glucose. At first the dose should not be above 0.5 sodium salicylate. This dose should be increased gradually never to more than 1.5-2 per dose. Salicylate of sodium, 2 grams twice daily, is sufficient usually to keep the organism under the influence of the drug.

There are many and the writer is one, who feel that the intravenous use of salicylate of sodium is hardly justifiable at the present time. He is unconvinced that the advantages outweigh the dangers. He may be overcautious, but intravenous treatment seems to him justifiable only when the result obtained is more or less specific and when it can be obtained by no other method. Much of the modern intravenous treatment seems to him unnecessary, meddlesome and even dangerous, besides being annoying, inconvenient and expensive to the patient.

The treatment of *septic infective endocarditis* is then reviewed. The authors are conservative as to the value of most of the methods of specific or nonspecific treatment. The treatment by cacodylate of sodium advised by Capps is wrongly described as intravenous instead of subcutaneous. With regard to *subacute malignant endocarditis* or that of

long duration the authors conclude that "the malady remains, in the present state of our knowledge, beyond the resources of therapy."

On the whole this volume is a remarkably clear, wise and vivid discussion of endocarditis. It is distinctly a clinical description with little discussion of the anatomical changes. As such there are few, if any, better articles on the subject in modern literature.

W. S. T.

NOUVEAU TRAITÉ DE PATHOLOGIE INTERNE. MALADIES DU COEUR ET DES VAISSEAUX. By Charles Laubry with the collaboration of Daniel Routier, J. Walser and Ed. Doumier. Paris, 1930 (one or two volumes), Doin & Cie.

This work (1,200 pages with 242 illustrations and 10 large color plates) is more than a pathological study; it is an attempt to classify diseases of the heart and blood vessels, to discuss etiology, symptoms, signs, functional disturbances, gross and microscopic pathology, treatment and prognosis. It is founded on the authors' own work and study; is carefully written, systematically arranged and well illustrated. At times one feels that the systematization is carried to the point where it becomes confusing rather than helpful, that a familiar subject (such as the arrhythmias) is being rewritten or that an important one (as thrombo-angiitis obliterans) is passed over rather lightly, but these are minor criticisms. The section on diseases of the blood vessels is particularly interesting, and throughout the book the beautiful illustrations, the emphasis on pathological findings and the fundamental good sense of the suggestions for treatment (even if one does not share the authors' faith in the value of iodides) make this a valuable book.

E. H.

HYPERTENSION. By Leslie T. Gager, M.D., Clinical Professor of Medicine at the George Washington University; Attending Physician Gallinger Municipal Hospital; Associate Physician George Washington University Hospital. Baltimore, 1930, 158 pages, Williams & Wilkins Co.

In this monograph a splendid exposition of the story of blood pressure from its inception to the present time has been accomplished. The book is very well written and thoughtfully conceived, so that it is a pleasure to read it and follow the writer's impression derived from the vast literature on this subject and from his practical experience. It is a great delight, for some of us at least, to find a clinician who is willing to acknowledge that functional pathology is of equal importance in the practice of the art of medicine with pathological anatomy, and that some conditions, e.g., hypertension, are diseases attributable to patho-

physiology and not to deviations from the normal that may be demonstrated to the eye or touch. In the development of his subject Gager has a singularly happy faculty in picking out the historical stepping stones that are both interesting and significant, so that this part of the work becomes a source of instruction instead of a dry category of dates and happenings as is so often the case. The review of the facts in regard to hypertension are exceedingly well enlled out, and the arguments pro and con on any doubtful point are fairly given. The generous statement that (p. 107) "As a matter of fact, it has been my experience that significant and lasting reduction in severe chronic hypertension is frequently impossible either by drugs, venesection or withdrawal of cerebro-spinal fluid," is refreshing in its sincerity and honesty; it corresponds to the experiences which all physicians have gone through and is vastly different from the impression created by many reports which advocate certain forms of treatment as being almost infallible. Gager has used potassium thiocyanate with satisfactory results in patients with uncomplicated genuine or essential hypertension; he has been largely responsible for the favorable reception this drug is receiving in this country. This volume on hypertension may be recommended to the physician who desires a review of this subject that embodies a thoughtful presentation, logical conclusions and a sparkling literary form that is rare in a medical book.

H. O. M.

RECENT ADVANCES IN CARDIOLOGY. By C. F. T. East and C. W. C. Bain. Philadelphia, 1929, P. Blakiston's Son & Co.

It is difficult indeed to restrain one's enthusiasm in writing of this small book. It is small only in comparison with the average textbook upon diseases of the heart, for it contains nearly three hundred and fifty pages, and is surprisingly complete. The authors have "tried to give a summary of the new knowledge, and also to describe its bearing upon problems which are not primarily cardiac." In a review so brief as this it is impossible to indicate how well they have succeeded, but of their success there can be no reasonable doubt. Not only have they given admirable summaries of recent advances in our knowledge of circulatory diseases, but they have also supplied that additional thing for lack of which so many attempts of this kind have failed, namely, a running critical commentary that is well-founded, authoritative, and refreshingly sane. The presentation is concise, as it must and should be, but ample space is devoted to every important phase of each subject; for example, such matters as the circus movement of auricular flutter and fibrillation are discussed in detail and with admirable clarity. The volume is not restricted to matters of diagnosis; general treatment and digitalis therapy are each given an entire long chapter.

From a series of chapters so uniformly excellent it would be gratuitous to select any one for particular praise, but one can scarcely neglect to mention the discussion of circulatory failure as distinguished from cardiac failure. Altogether, the volume is one to be commended without hesitation to all who wish to bring their knowledge of cardiology up to date. It is superior in almost every respect to many of the textbooks now available.

H. M. M.

The American Heart Journal

VOL. VI

APRIL, 1931

No. 4

Original Communications

INTERPRETATION OF BUNDLE-BRANCH BLOCK BY MEANS OF THE MONOCARDIOGRAM*

HUBERT MANN, M.D.
NEW YORK, N. Y.

THE diagnostic distinction between right and left bundle-branch block in human beings is still uncertain. Lewis and his co-workers have attempted to apply their experimental work on animals to the diagnosis of human bundle-branch block, but their conclusions have been at variance with much clinical and pathological evidence and have failed of general acceptance.

This paper is an attempt to show that, by means of a method of analysis previously described,¹ it is possible to determine right and left bundle-branch block in a manner which is consonant with the clinical, experimental and pathological findings. This method of analysis is based on the fact that the three separate leads of the electrocardiogram are merely a conventional method of recording one single series of electrical phenomena. The heart itself does not produce the three separate cardiographic curves which we designate Leads I, II and III, but these curves are derived from a single series of phenomena and constitute a conventional and convenient method of observing and recording these phenomena. W. Einthoven² and many others have recognized this and have discussed the significance of the threefold electrocardiogram.

It is readily understandable that the ordinary electrocardiogram which is spread out on a time axis is admirably adapted to the portrayal and analysis of cardiac arrhythmias because time relations play an important part in such analyses. On the other hand the determination of the site of anatomical, physiological and pathological changes in the heart has been difficult because of the unsuitability of the ordinary electrocardiogram to this end. The curves could be made much better suited to the delineation of these spatial relationships if instead of spreading them out on a time axis (and thereby sacrificing spatial

*From the Cardiographic Department of Mount Sinai Hospital, New York City.

relationships) we could spread them out spatially (thereby neglecting the time relationship).

A way of doing this was worked out mathematically by Einthoven, Fahr and deWaart,³ but it has proved to be a very difficult and cumbersome method. In 1916 an encounter with the difficulties of this method led me to devise a method of analyzing the electrocardiogram¹ which gave instead of three leads a single curve or monocardio-gram, the axes of which had a spatial significance. This monocardio-gram is really a fusion of the three leads of the electrocardiogram into a single curve by an algebraic reversal of the process by which three leads are obtained from one heart. The derivation of this single curve

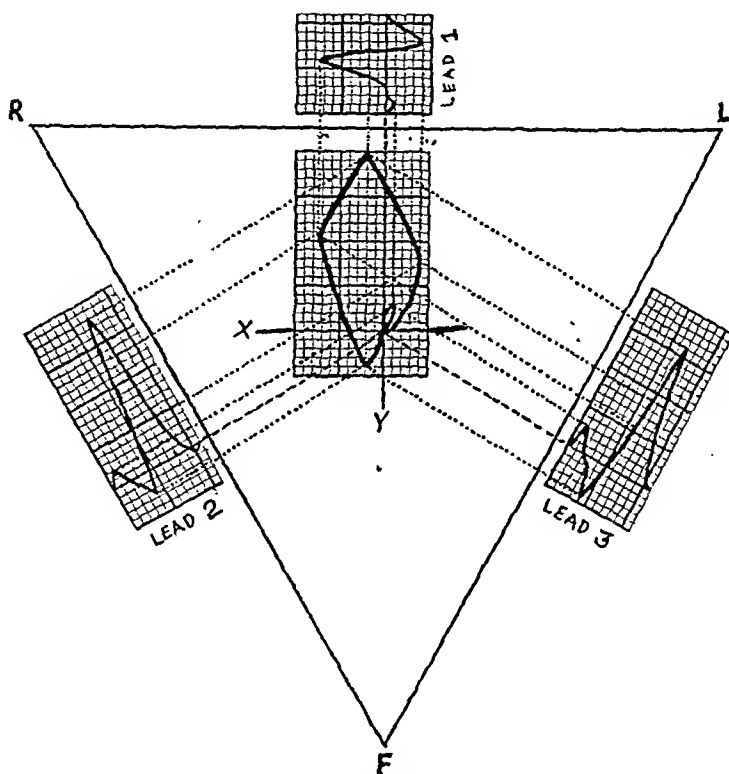


Fig. 1.—This shows the monocardio-gram which is derived from an electrocardiogram published by Einthoven⁴. It can be seen that the three leads of the electrocardiogram are really derivatives of the monocardio-gram, obtained by successive projections of the monocardio-gram on the three sides of the equilateral triangle.

Note that in this monocardio-gram, as in all others shown in this article, the right side is on the observer's left. This is in accordance with the ordinary usage in regard to Einthoven's triangle and facilitates interpretation.

or monocardio-gram was at first purely theoretical and mathematical, but in 1925 I succeeded in devising an experimental apparatus* for obtaining and recording this monocardio-gram directly from the patient, thereby adding further proof of the validity of the method.

The method of deriving such a single curve or monocardio-gram can be made clear by reference to Fig. 1. This illustration shows the main deflection in the three leads of an electrocardiogram originally pub-

*This apparatus, called a monocardigraph, was developed with the aid of a grant from the Rockefeller Institute and a description of it will soon appear.

lished by Einthoven.⁴ These three leads are here shown arranged parallel to the sides of an equilateral triangle in such a way that the projections of the three base lines meet at the center of the triangle. Under these conditions the projections of simultaneous instants of the three leads meet at points which, taken successively, constitute a single curve or monocardio-gram. The reasons why this particular construction is adopted are made clear in my original paper (q.v.) and depend on the fact, as elucidated by Einthoven, that the projections on the sides of an equilateral triangle of any straight line drawn within the triangle have a relationship similar to the relationship existing between the leads of an electrocardiogram.

The production of a single curve from the three leads of an electrocardiogram is more than a mathematical or geometrical *tour de force*. Fig. 1 provides a clear and comprehensive diagram of the manner in which three leads are derived from the single series of electrical phenomena taking place in the heart. The central curve or monocardio-gram represents graphically the electrical phenomena which occur during successive instants (hundredths of a second) throughout the duration of the main deflection, while the three leads can be considered as merely the projections of this central curve on the three sides of a triangle. They are really like three shadows of the central curve, thrown in three different directions.

But while the shadows are spread out in time the central curve is spread out in space. When this curve is to the right and above the zero point, it indicates that the center of negativity* is to the right and above the electrical center† of the heart. When the curve moves to the left of the zero point it indicates that the center of negativity in the heart has shifted to the left. Thus the monocardio-gram affords us a method of localizing in a plane various parts of the cardiac musculature, of analyzing an electrocardiogram with regard to its anatomical significance, of determining what part of the cardiac musculature is responsible for various types of bizarre and abnormal electrocardiograms, of locating the site of origin of extrasystoles, etc.

A consideration of the method of analysis here outlined will make plain that every properly taken electrocardiogram carries in itself the possibility of being reduced to a single curve or monocardio-gram and that this single curve can make evident a number of hitherto concealed anatomical and spatial relationships. Numerous questions as to the site and extent of myocardial damage following acute coronary artery

*Center of negativity is defined in the original description of the monocardio-gram as follows: "If at any moment there are present in the heart several (negative) electrical charges which have value (intensity, voltage) and position (direction) then the center of negativity is that point which represents the algebraic sum of all the potential differences."

†The electrical center of the heart is the point which is represented by the center of the equilateral triangle. It may be defined as that point at which an electrical charge will produce no deflection in any lead of the electrocardiogram.

occlusion can be answered by means of this method of analysis. The determination of the site and extent of the lesions which produce electrocardiographic changes of the type known as intraventricular conduction defect or arborization block can be studied by this method. The exact nature of fibrillation and flutter and the location of the circus stimulation in flutter can be studied. The nature and significance of ventricular preponderance and its relationship to ventricular hypertrophy and to changes of position of the heart can be made clear.

Much of my previous study has been based upon monocardigrams derived from electrocardiograms. Such curves, however, are open to

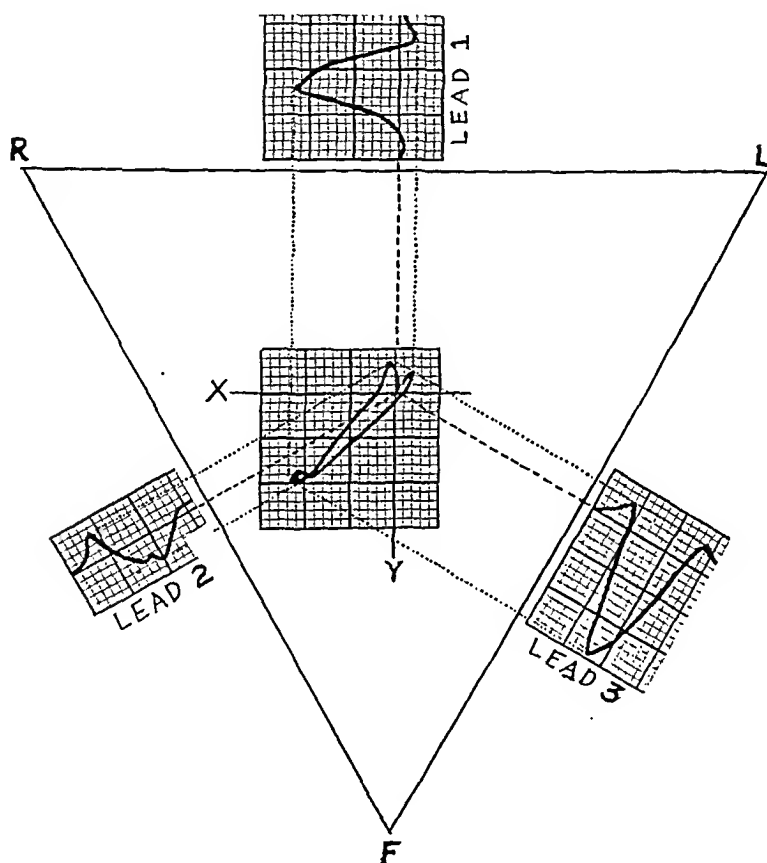


Fig. 2.—This shows the monocardigram derived from an electrocardiogram published by Lewis (*Clinical Electrocardiography*, London, 1913, p. 31). Note that in this illustration the monocardigram is mainly to the right (the observer's left) of the zero point while in Fig. 3 the curve is mainly to the left (the observer's right) of the zero point.

the criticism that they are theoretical and artificial and have no real basis in fact. The development of an instrument by means of which the monocardigram can be recorded directly from a patient without the necessity for any intermediate electrocardiogram has removed these objections.

Much of the theoretical work of the past ten years must be supplemented with actual graphic records before our material is ready for publication but in the matter of bundle-branch block the curves are

so obvious and unequivocal that their analysis does not involve any appreciable doubt.

Inasmuch as most of the confusion about bundle-branch block has arisen from the work of Sir Thomas Lewis I have taken as typical instances of bundle-branch block the two curves which he published in his textbook, *Clinical Electrocardiography* (London, 1913, page 31). These curves are similar to present-day curves except that time intervals are indicated in thirtieths of a second. Each of these curves has been analyzed in a manner similar to that illustrated by Fig. 1, and the resulting monocardigrams are presented in Figs. 2 and 3.

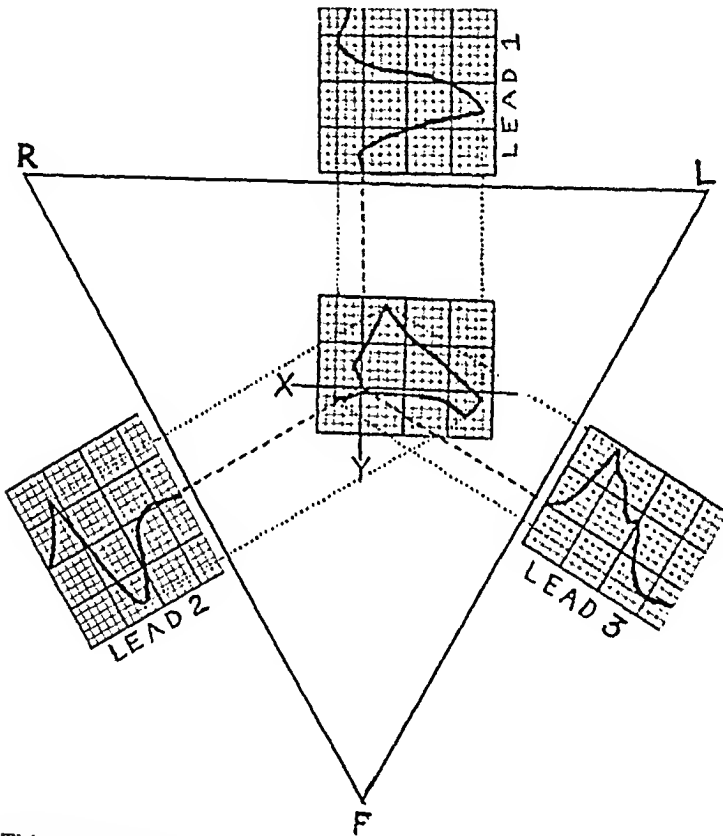


Fig. 3.—This shows the monocardigram derived from an electrocardiogram published by Lewis (*Clinical Electrocardiography*, London, 1913, p. 31). Note that this monocardigram is mainly to the left (the observer's right) of the zero point.

It can be seen at once that these two monocardigrams differ considerably from the normal as represented in Fig. 1. In Fig. 2 which is derived from an electrocardiogram which, according to Lewis indicates "functional defect of the right division of the auriculo-ventricular bundle," the monocardigram shows a shift of the center of negativity downward and to the right. In Fig. 3, derived from an electrocardiogram which, according to Lewis, indicates "functional defect of the left division of the auriculo-ventricular bundle," the monocardigram shows a shift of the center of negativity to the left.

That this shifting of the center of negativity in bundle-branch block is a constant phenomenon is shown by Figs. 4 and 5 which show the

monocardiograms of two instances of bundle-branch block which were recorded in the cardiographic laboratory of Mount Sinai Hospital. The same obvious shifting of the center of negativity is shown: one to the right and the other to the left.

Now it is practically self-evident that in the human heart any delay or block in the excitation of the left ventricle will result in a shifting of the center of negativity toward the right and that, conversely, a delay or block in the excitation of the right ventricle will shift the center of negativity toward the left side. It is also obvious that in right bundle-branch block the excitation of the right ventricle is de-

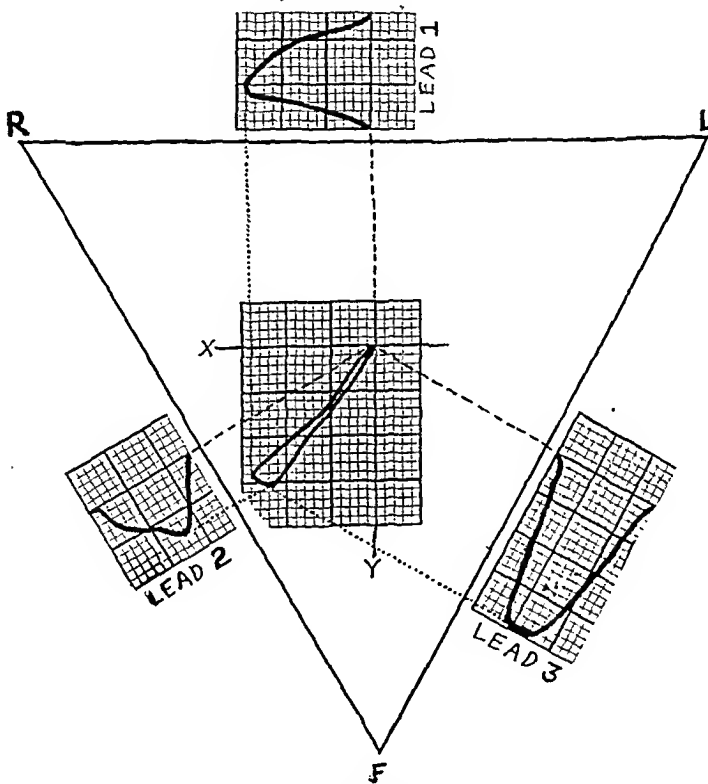


Fig. 4.—Monocardiogram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Fig. 2. The original electrocardiogram is shown in Fig. 7-A.

layed and that in left bundle-branch block the excitation of the left ventricle is delayed. The analysis of such curves by the monocardiogram shows clearly that in right bundle-branch block the electrocardiogram shows an inverted main deflection in Lead I while in left bundle-branch block the main deflection is upright in Lead I.

The criteria then for bundle-branch block may be defined thus:

Electrocardiograms which indicate bundle-branch block exhibit the following characteristics:

1. A main deflection which shows a width of at least twelve hundredths of a second, good amplitude and smooth contour.

2. A T-wave which is opposite in direction to the main deflection and which is practically a continuation of the main deflection without any definite iso-electric transition period.
3. Right bundle-branch block is indicated by an inverted main deflection in Lead I and an upright main deflection in Lead III.
4. Left bundle-branch block is indicated by an upright main deflection in Lead I and an inverted main deflection in Lead III.

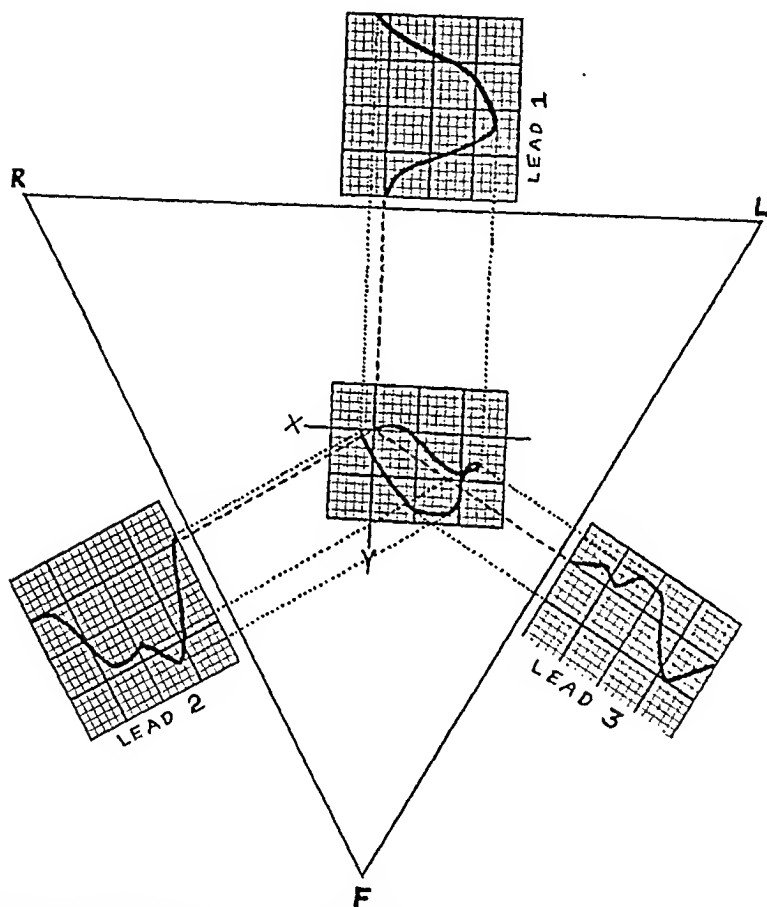


Fig. 5.—Monocardiogram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Fig. 3. The original electrocardiogram is shown in Fig. 7-B.

Points 1 and 2 summarize the generally accepted characteristics of bundle-branch block. Points 3 and 4 summarize our interpretation of right and left bundle-branch block and their differentiation.

It is not the purpose of this paper to discuss critically all the evidence in favor of this interpretation. It will suffice here to mention that left bundle-branch block occurs more than ten times as frequently as right bundle-branch block, which is in accord with the fact that post-mortem examination usually reveals localization of the myocardial damage in the left ventricular musculature. To any one who has seen instances of the gradual evolution of electrocardiograms from

fairly normal to the type characteristic of intraventricular conduction defect and then toward the type which is characteristic of left bundle-branch block it seems quite superfluous to point out that the progressive injury is practically always located on the left side.

As this paper was approaching completion a very apt illustrative case presented itself. The patient, a man of sixty years, evidently extremely ill, had an electrocardiogram which we regard as characteristic left bundle-branch block. The monocardigram shown in Fig. 6 is like Fig. 2 and Fig. 4. Post-mortem examination revealed an

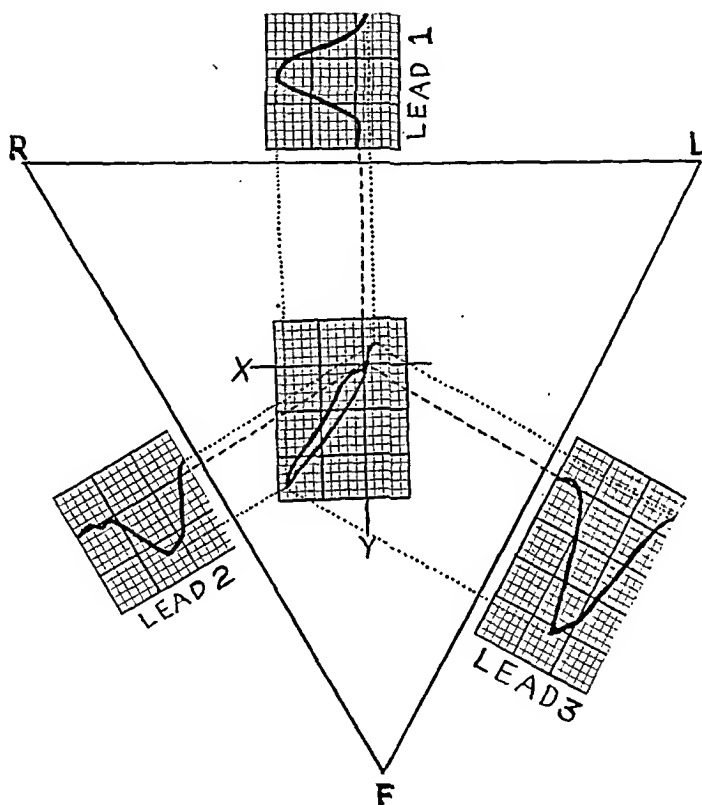


Fig. 6.—Monocardigram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Figs. 2 and 4. The original electrocardiogram is shown in Fig. 7-C.

enormous organized thrombus adherent to the left septum and the anterior wall of the left ventricle with extensive destruction and fibrosis of the myocardium of the left side of the septum and the anterior wall of the left ventricle. There was narrowing of the left coronary artery at its origin. There was a relatively tiny thrombus at the very apex of the right ventricle with no extensive gross damage to the right ventricular musculature.

The coincidence of extensive destruction in the region of the left bundle branch with a definite ante-mortem diagnosis of left bundle-branch block was striking. Were it the only instance in which such a

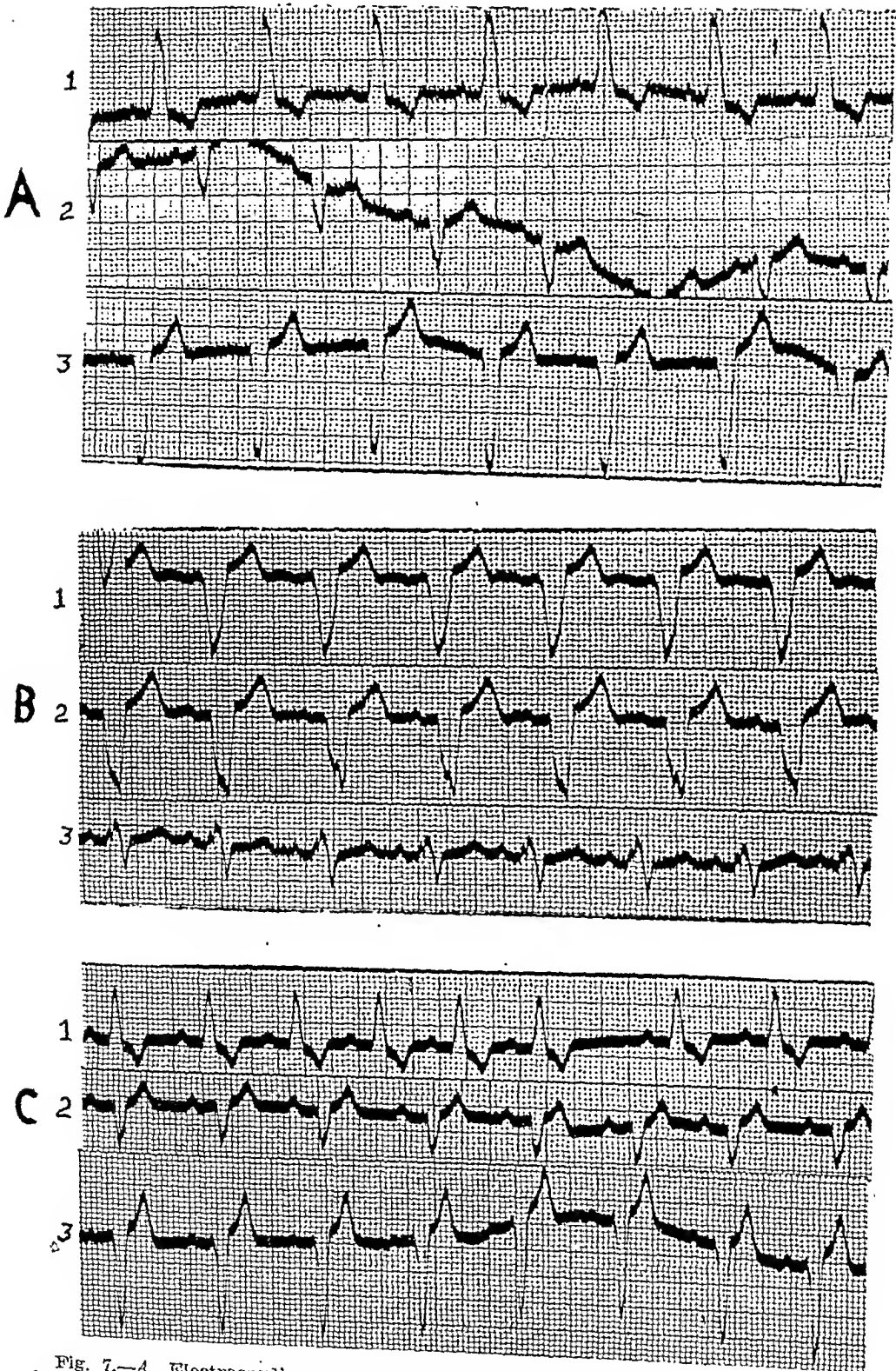


Fig. 7.—A, Electrocardiogram from which monocardigram shown in Fig. 4 was derived. B, Electrocardiogram from which monocardigram shown in Fig. 5 was derived. C, Electrocardiogram from which monocardigram shown in Fig. 6 was derived.

coincidence was observed it could hardly be regarded as convincing evidence. But we have repeatedly seen the association of this type of electrocardiogram with a gross lesion involving exclusively the left ventricle. The service of any large active hospital will provide numerous similar cases.

As to the reasons for the earlier errors in the interpretation of right and left bundle-branch block it should be pointed out that the conclusions derived from experiments on the canine heart should not be applied to the human heart without taking into consideration the marked differences between canine and human hearts in regard to both the position of the anatomical axes and the angle of the interventricular septa. In the experimental work performed on a rhesus monkey and reported by Lewis⁵ the monkey's normal electrocardiogram shows a decided tendency toward right ventricular preponderance, a condition which tends to invalidate the applicability of the results to the human heart.

As early as 1916 the question of right and left bundle-branch block was a moot one. By 1917 these monocardigraphic studies, supported by their correlation with numerous post-mortem observations, seemed sufficiently conclusive to justify routinely reporting the localization of bundle-branch block in a manner opposite to the published interpretation of Lewis. Within the past ten years and especially within the past few years numerous writers have dissented from the "orthodox" interpretation. The experience which we have derived from the monocardigram since its employment in 1917 is now adequate to warrant publication in the hope that the weight of evidence, experimental, clinical, anatomical and statistical, will soon succeed in bringing the general interpretation of bundle-branch block into agreement with the facts. Old errors cling stubbornly and it is at times necessary to remind ourselves that while truth may be a bitter pill it is a good physic.

SUMMARY

1. The article describes a method of analyzing the electrocardiogram by a fusion of the three leads into a single curve or monocardigram.

2. This method of analysis brings out anatomical and spatial relationships hitherto concealed and facilitates the investigation of such problems as the site and extent of myocardial and coronary lesions, the nature of fibrillation and flutter and the sites of origin of extrasystoles.

3. It is peculiarly well adapted to the diagnosis of right and left bundle-branch block.

4. Numerous applications of this method of analysis show that in right bundle-branch block the electrocardiogram has an inverted main

deflection in Lead I while in left bundle-branch block the main deflection is upright in Lead I.

5. The reasons for previous misinterpretations are discussed briefly.

The writer wishes to acknowledge his indebtedness to Dr. M. A. Rothschild and Dr. George Bachr for their suggestions and encouragement in the preparation of this paper.

REFERENCES

1. Mann, H.: *Arch. Int. Med.* 25: 283, 1920.
2. Einthoven, W.: *Lancet* 1: 853, 1912.
3. Idem, Fahr, G., and deWaart, A.: *Arch. f. d. ges. Physiol.* 150: 275, 1913.
4. Einthoven, W.: *Lancet*. *Loc. cit.*, Fig. 8.
5. Lewis, T.: *Philosophical Transactions B.* 207: 287, 1916.

THE EFFECTS OF DIGITALIS ON PREMATURE AURICULAR
CONTRACTIONS ASSOCIATED WITH ATTACKS OF PAR-
OXYSMAL AURICULAR FIBRILLATION. THE USE
OF THE DRUG IN THE TREATMENT AND PRE-
VENTION OF CERTAIN FORMS OF THESE
ARRHYTHMIAS*

SIDNEY P. SCHWARTZ, M.D.
NEW YORK, N. Y.

INTRODUCTION

AURICULAR fibrillation, ushered in with a very rapid ventricular rate varying between 150 and 250 beats per minute and not slowing with rest, is one of the most severe forms of this type of irregularity in patients with established heart disease and signs of congestive heart failure. It is one of the few disturbances of the cardiac mechanism which, if left untreated, may result in symptoms and signs grave enough to cause death within a comparatively short time after its onset.

Within the last few years there have been admitted to the wards of the Montefiore Hospital a group of seven such patients with advanced organic heart disease and signs of congestive heart failure who have been subject to frequent attacks of auricular fibrillation with a persistently high ventricular rate. These attacks were invariably preceded for from one to three days by premature auricular contractions first coming on singly, then in groups of two or more. From prolonged observation of these patients under controlled conditions and a variety of experiments carried out on them it has been noted that almost all showed restoration to normal sinus rhythm when they were given single large doses of digitalis within a comparatively short time after the auricular fibrillation was recognized. In all of these instances, the administration of adequate and judicious doses of digitalis during their periods of normal sinus rhythm could prevent the onset of the premature auricular beats, and prevent the appearance of auricular fibrillation. Even after the premature auricular beats set in, it was possible to abolish them and to restore sinus rhythm with digitalis. In every instance a relatively slow sinus rate could be maintained after normal rhythm had been established by the effective use of digitalis.

*From the Medical Division of the Montefiore Hospital for Chronic Diseases, New York City.

Because of the close relationship that exists between the administration of digitalis and the restoration of normal sinus rhythm following the onset of premature auricular beats as well as between the use of digitalis and the prevention of recurrences of auricular fibrillation, with the accompanying signs of severe congestive heart failure, these patients form a distinct group among the large number of subjects with auricular fibrillation and from the point of view of treatment should be given special consideration.

Three of these cases are reported in detail in order to call attention to the characteristic sequence of events that takes place following the onset of these irregularities and their response to variable dosages of digitalis.

REPORT OF CASES

CASE 1.—S. J., a female, aged 30 years, was admitted to the Montefiore Hospital on Aug. 6, 1927. Her chief complaints were shortness of breath, precordial distress, weakness and swelling of the lower extremities.

Previous Illness.—She suffered her first attack of rheumatism at the age of 20 years. At 24, she was informed that she had heart trouble. Seven years ago (January, 1923) the patient began to notice for the first time that emotional disturbances upset her a great deal. Following a quarrel or a crying spell and at times shortly after least exertion she would become conscious of her heart beating very rapidly.

At first she would feel isolated thumps of her heart against her chest wall. Within one to two hours she would be conscious of their increase in frequency. As she felt and counted her pulse and noticed that it increased in frequency and irregularity, she would find herself breathing with difficulty. At the height of an attack she began to feel precordial distress. At first the precordial pains were localized in the region of the left fifth intercostal space near the mid-clavicular line, but as the attack increased in severity, the pains radiated to the left shoulder and to the inner side of the left arm, and finally she felt the pains in the smaller fingers of the left hand.

Nothing would relieve her pains or the shortness of breath except the adequate administration of digitalis. (These were the patient's own observations.) She could predict almost with regularity when the attacks would cease by the way she responded to this particular drug. With the slowing of the heart rate she would begin to lose her precordial distress, her breathing would become easier, and within one to three days she could again count her regular pulse rate if she had received a "strong dose of digitalis."

Physical examination on admission to the Montefiore Hospital revealed a poorly nourished female complaining of difficulty in breathing. There was intense cyanosis of the lips, cheeks and ears. The superficial vessels of the neck were markedly distended. The apical impulse of the heart was in the fifth intercostal space in the region of the midclavicular line. A short rough systolic murmur followed by a prolonged diastolic murmur could be heard as far down as the xiphoid region. The heart rhythm was totally irregular and averaged 120 beats per minute. There was a pulse deficit of an average of 30 beats per minute. The blood pressure was 145 mm. of mercury systolic and 60 mm. diastolic.

The lungs showed dullness with absent breath sounds over the right base posteriorly from the angle of the scapula to the base. Many moist râles were heard at the left base posteriorly. The liver edge was palpable 3 cm. below the costal margin. There was moderate swelling of the lower extremities.

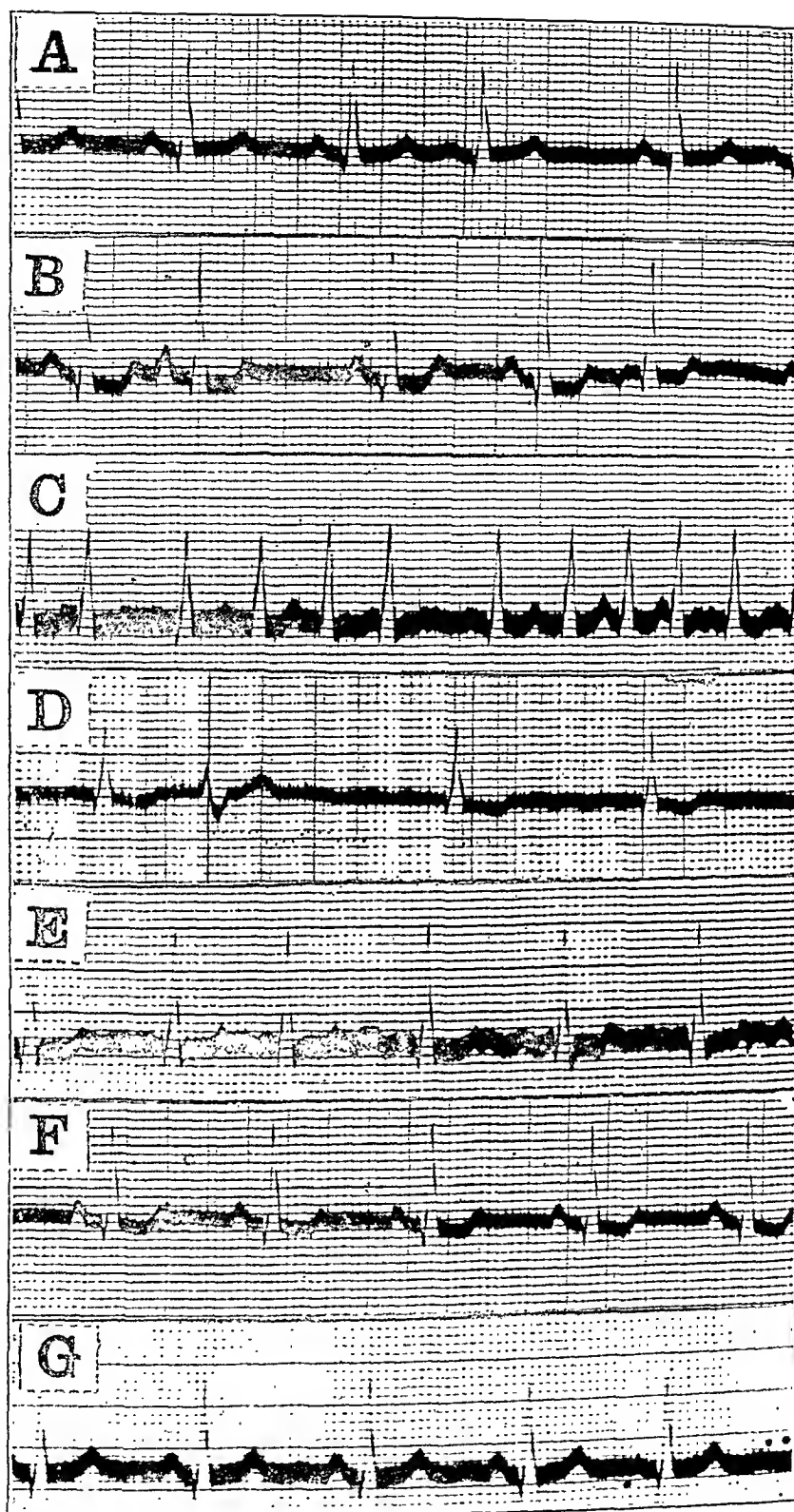


Fig. 1.—Case 1. A series of serial electrocardiograms, Lead I only, showing the appearance of successive changes in rhythm starting with (A) Sinus arrhythmia and premature auricular beats with an average ventricular rate of 100 beats per minute; (B) bigeminal rhythm due to premature auricular beats with an average ventricular rate of 148 beats; (C) a seizure of paroxysmal auricular fibrillation with a rapid ventricular rate; (D) alternate premature ventricular beats and partial block following the daily use of 3 e.e. of digitalis for seven days after the onset of auricular fibrillation, showing the perpetuation of auricular fibrillation with small daily doses of digitalis; (E) auricular fibrillation with a ventricular rate of 75 beats per minute four days after the preceding record and after the withdrawal of digitalis; (F) restoration to normal sinus rhythm, record taken on same day as above; (G) fifteen days later, the beginning of another attack with the appearance of premature auricular beats.

Course and Progress.—On admission, the patient was put to bed and promptly given 3 c.c. of the tincture of digitalis to control her ventricular rate. Five days later a thoracentesis of the right chest yielded 1200 c.c. of clear straw colored fluid. With continued rest and further digitalization (3 c.c. daily) she felt better at the end of seven days. The edema of the legs disappeared, the liver edge was no longer palpable, she became free from dyspnea, and the heart rate had slowed to an average of 70 beats per minute. It was noticed, however, that at the end of nine days after she had received a total of 27 c.c. of the tincture of digitalis, she showed partial heart-block with a basic ventricular rate of 44 and bigeminal rhythm due to alternate premature ventricular beats of the ventricle. At this time all medication was discontinued.

An electrocardiogram taken on Sept. 12, 1927, about one month after her admission revealed the presence of sinus rhythm. This unusual sequence of events interested me very much, and the patient was watched from day to day and studied very carefully with the idea of determining, if possible, whether the return to sinus rhythm was spontaneous or whether it was actually due to the use of digitalis.

One month later (Oct. 12, 1927) following an exciting debate with her roommate, the patient began to complain of irregular heart action and shortness of breath. Examination on that day revealed coupled rhythm with irregular heart action averaging 120 beats, but without any pulse deficit. These extra beats came at times singly, at other times in groups of two, and once in every five minutes groups of three could be counted interrupting the basic rhythm.

Repeated electrocardiograms taken through the day revealed premature auricular beats but a basic sinus rhythm. This irregularity of the heart was a persist for six hours, at the expiration of which time the patient was to complain of shortness of breath and a tender I. The administration of a single dose of 15 c.c. of markedly of nature a 4 beats per averaged 54 and about time.

On Oct. 25, 1927, at 3:40 P.M. the patient of breath and irregular action of the heart. preceded by isolated premature auricular beats. Most of these beats had a compensatory. The heart rate was was distinctly coupled. The patient began to breathe with difficulty. Large beads of perspiration appeared. The ventricular rate averaged 210 beats per. certainty that auricular fibrillation was. Four hours after the onset of this seizure level of the umbilicus and it was painful a

A dose of 10 c.c. of the tincture of digitalis and within the next four hours her heart rate per minute. It was regular on the following morning in breathing because during this seizure fluid in pleural cavity. Three days later, she was up and

Between Oct. 25, 1927, and Jan. 31, 1929, at which permanent auricular fibrillation, she was seen and studied seizures of these arrhythmias. Innumerable electrocardiograms during and subsequent to these attacks revealed a definite sequence of events for each attack and these I wish to discuss.

Emotional disturbances were the principal precipitating factors. Each seizure would be ushered in with premature auricular beats at first coming on singly and then in groups of two and three. As these became more frequent the ventricular rate would approximate 150 beats per minute and be irregular. The administration of a large dose of digitalis given at this time would gradually slow the ventricular rate, the premature beats would disappear, the patient's symptoms of breathlessness would subside, and the arrhythmia would pass away without fibrillation of the auricles setting in. During the presence of sinus rhythm the appearance of premature auricular beats could almost invariably be prevented by the daily use of a sufficient quantity of the drug to maintain sinus slowing. As the effect of the drug would wear off, the whole sequence of events described above would repeat itself.

The administration of a small daily dose of digitalis during the presence of established auricular fibrillation would invariably perpetuate the auricular fibrillation and cause heart-block with multiple premature beats of the ventricle indicating the toxic effects of the drug. It was only during the effective exhibition of a large dose of digitalis at one time that the fibrillation would pass off.

The auricular fibrillation was allowed to continue for several days at a time in order to note the effects on the symptoms and signs. Each time this was done, after about three days, following the onset, dyspnea would become extreme, the liver edge would get large and tender, and pulmonary edema with swelling of the legs would become evident. The high ventricular rate persisted even after the use of large doses of opiates. The longest period during which this patient was allowed to maintain this high ventricular rate was seven days. At this time the administration of a 15 c.c. dose of digitalis at one time resulted after two days in the restoration of sinus rhythm. The symptoms of congestive heart failure following the onset of her irregularities cleared up within five days after the establishment of sinus rhythm.

Finally the auricular fibrillation was allowed to continue for a period of several days again, when the intravenous use of digitalis was instituted to determine whether the rhythm would return to normal more quickly by this method than by the oral administration. Nine c.c. of digifolin were given to her at one time intravenously. The heart rate slowed two hours later which was about two hours sooner than when the drug was given orally, but the return to normal sinus rhythm did not take place until two days after that.

Permanent auricular fibrillation set in on Jan. 31, 1929, and shortly afterwards the patient died in severe congestive heart failure.

CASE 2.—C. K., a female, aged 59 years, was admitted to the Montefiore Hospital on Aug. 8, 1928. Her chief complaints were shortness of breath on exertion and recurrent attacks of severe palpitation of the heart. These symptoms were of approximately two years' duration.

Previous Illness.—The patient had been well until five years ago (June, 1925) when during convalescence from pneumonia she began to notice, for the first time, breathlessness on exertion.

In the winter of 1927 she experienced fainting sensation, following excitement and exertion such as scrubbing floors or walking up a flight of stairs. On rest and "medication" she overcame these difficulties, but there were recurrences of symptoms in March, 1928. In April, 1928, a severe attack of vomiting in addition to her other complaints compelled her to seek admission to the People's Hospital where she remained for three weeks and improved considerably under rest and medication. She had been at home since her discharge from that hospital.

Physical examination on admission to the Montefiore Hospital revealed a fairly nourished woman, severely dyspneic, with marked cyanosis of the face, lips, ears and hands. There was distention of the superficial vessels of the neck. Her chest

was barrel shaped. The apical impulse of the heart was not palpable, and percussion of the cardiac outlines was unsatisfactory. The heart sounds were of poor quality. The rhythm was totally irregular and averaged 182 beats per minute. There was a pulse deficit of 32 beats. The blood pressure was 180 mm. of mercury systolic and 120 mm. diastolic. There was dullness at the left base posteriorly with many moist râles that were heard all over the chest as far up as the level of the angle of the scapulae on both sides. The liver edge was palpable 3 cm. below the costal margin in the midclavicular line. There was swelling of the lower extremities.

The signs of congestive heart failure were attributed in part to the untreated irregularity which was confirmed by electrocardiograms to be that of auricular fibrillation.

Course and Progress.—On her first day in the hospital, the patient was given 9 c.c. of the tincture of digitalis in one dose. Because of her unusual history of attacks of palpitation which responded to medication at home, she was watched very carefully. Three days after the administration of a single dose of digitalis, her

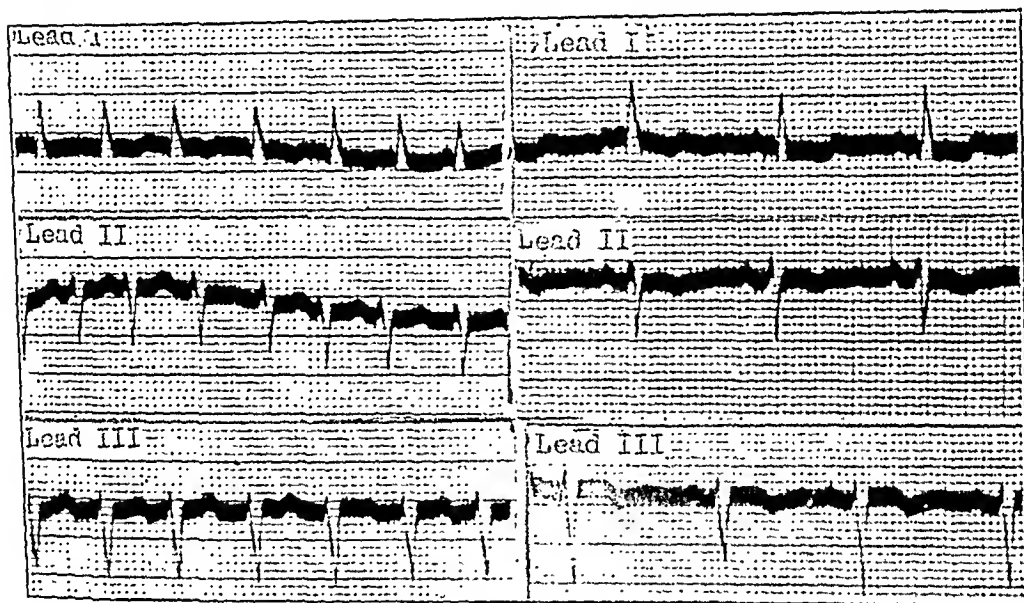


Fig. 2.—Case 2. Comparison records before and after the administration of a single dose of 12 c.c. of digitalis. Note the almost regular rapid ventricular rate during the presence of auricular fibrillation. The rate and rhythm returned to normal, three days after the drug was given.

heart rate and rhythm returned to normal, her dyspnea and cyanosis had disappeared, the swelling of her extremities had subsided, and the patient begged to be allowed out of bed. Between the time she had received her first dose of digitalis on Aug. 9, 1928, and the second week of September, 1928, the patient was kept off all medication except a mild laxative which she was allowed in daily doses.

Examination on Sept. 15, 1928, revealed that she was slightly dyspneic even at rest and that her heart rhythm was irregular, averaging 118 beats per minute. It was interrupted by many premature beats with compensatory pauses which were confirmed by the electrocardiograms to be auricular in origin. Four hours later, following the administration of 8 c.c. of digitalis almost all of the premature beats disappeared, the heart rate diminished to 90 beats per minute and on the following morning it was 65 and regular.

She remained well until Oct. 31, 1928, when I was notified that following some excitement and exertion she experienced a fainting spell for which she was put to bed. Examination at 11 A.M. of that day showed her to be severely dyspneic and

cyanotic with her neck vessels pulsating tumultuously. The heart rhythm was almost regular but varied in rate between 210 beats per minute and 240 beats. Clinically it was very difficult to be sure that auricular fibrillation was present, but electrocardiograms taken then confirmed the presence of the arrhythmia.

Four days after the onset of this irregularity, the patient was given 12 c.c. of digitalis orally, which she was able to take only with difficulty. On the following morning, her apical rate was still irregular, but it now averaged only 100 beats per minute. Two days later (Nov. 5, 1928), electrocardiograms revealed the presence of sinus rhythm. After the establishment of the regular rhythm the patient was given a daily dose of 3 c.c. of the tincture of digitalis, and within 10 days she was clear of all her signs and symptoms of congestive heart failure that had developed very rapidly during the presence of the arrhythmia. The pulmonary edema had disappeared, the liver edge had receded to its original level of 2 cm. below the costal margin, the ascites and the swelling of the legs had all passed away.

In the ensuing few weeks, the patient was watched even more carefully than previously in order to see whether it would be possible to determine the causative factors and the mode of onset of her irregularities.

Exactly 16 days after she received her last dose of digitalis, she began to complain of shortness of breath which was more marked than previously. Her heart rate was irregular and averaged 110 beats per minute. A diagnosis of premature beats with compensatory pauses was confirmed by the electrocardiograms to be of auricular origin. A dose of 8 c.c. of digitalis abolished the arrhythmia and caused a slowing of the sinus rate to 56 beats per minute within 5 hours after its administration.

Between Dec. 4, 1928, and June 12, 1929, the date of her discharge from the hospital, the patient received daily doses of digitalis varying from 1 to 3 c.c. and never experienced any further attacks of irregularity of the heart. Throughout all this time, her ventricular rate was always about 60 beats per minute.

CASE 3.—S. R., a female, aged 61 years, was admitted to the Montefiore Hospital on Dec. 21, 1928. Her chief complaints were recurrent periods of shortness of breath associated with palpitation of the heart and weakness.

Previous Illness.—In the summer of 1928, the patient began to notice shortness of breath on moderate exertion and swelling of the lower extremities which has persisted since. In August, 1928, she became conscious of recurrent attacks of palpitation of the heart some of which would last as long as 5 hours and were frequently relieved by the continuous use of "green drops" prescribed for her by her physician. On Oct. 23, 1928, she entered the Presbyterian Hospital because of rapidly progressive swelling of the abdomen and lower extremities, shortness of breath and yellow discoloration of the skin.

Physical examination at that institution revealed a poorly nourished, deeply jaundiced old woman lying quietly in bed without dyspnea or cyanosis and looking chronically ill. The heart was enlarged both to the right and to the left sides, the apical impulse being in the sixth intercostal space in the anterior axillary line. Over this region there was a soft systolic murmur. A2 was accentuated. The heart rate was totally irregular.*

The lungs showed many moist râles at both bases posteriorly. The abdomen was large and there was shifting dullness. The liver and spleen were not palpable. There was moderate swelling of the lower extremities.

Shortly after her admission to the Presbyterian Hospital, a paracentesis of the abdomen was performed at which 3000 c.c. of opaque, yellow colored fluid were removed at one time.

*No note was made at the Presbyterian Hospital as to whether there was a pulse deficit present. However, it is definitely reported in this patient's chart that the irregularity was believed to have been due to premature auricular beats.

Between Oct. 23, 1928, and Dec. 6, 1928, she required three separate paracenteses of the abdomen for the relief of ascites. On her admission to the Montefiore Hospital, the patient still showed signs of dropsical effusion in both the pleural and abdominal cavities, and the heart rhythm was totally irregular, the ventricular rate averaging 120 beats per minute with a pulse deficit of 16 beats. Following rapid "digitalization" (16 c.c. in two days) the patient improved considerably so that within a few days after her admission, she was fairly comfortable. Particular note was made at this time (Dec. 24, 1928) that her heart rhythm had become regular and averaged 80 beats per minute.

Reëxamination on Jan. 18, 1929, approximately three weeks after the return of the sinus rhythm, revealed no evidence of any dyspnea, cyanosis, edema, or jaundice. The apical impulse of the heart was in the sixth intercostal space to the left of the midclavicular line. There was a short systolic murmur at the apex. A2 was accentuated. The heart rate was regular. The blood pressure was 190 mm. of mercury systolic and 90 mm. diastolic. The abdomen was soft and there was no evidence of shifting dullness. The liver edge was 4 cm. below the costal margin at the midclavicular line. The spleen was palpable 2 cm. below the costal margin. The legs showed slight pretibial edema.

Within one week the patient became ambulatory. She was able to be up and about until the morning of Feb. 8, 1929, when she had a severe attack. The electrocardiograms taken on this day showed auricular fibrillation with a very rapid ventricular rate. She received 9 c.c. of digitalis in one dose, and within two days there was a return to normal sinus rhythm and a disappearance of all symptoms of shortness of breath and signs of congestive heart failure.

For the next month she was placed under controlled observations, and repeated electrocardiograms were taken to determine, if possible, whether there was any relationship between the return of her symptoms and the onset of her irregularities and the disappearance of the digitalis from her system as judged by a return to normal of the S-T interval and the size, shape and form of the T-waves.

Changes in her rhythm, such as marked shifting of the pace-maker and the appearance of auricular premature beats, were observed to come on 17 days after she received the last dose of 9 c.c. of digitalis. At this time there was still evidence of negativity of the T-waves in Leads I and II, indicating probably that not all of the digitalis had been eliminated. During the presence of sinus rhythm it was possible definitely to maintain a relatively slow sinus rate by daily doses of 2 c.c. of digitalis.

From February, 1929, until May, 1929, the patient was ambulatory and did not require any further mechanical removal of fluids.

On the morning of May 14, 1929, the patient began to complain of breathlessness. She had not received any digitalis in the week prior to that time. Multiple auricular premature beats were found to interrupt and increase her ventricular rate. She was advised to stay in bed, and for the next two days there was a noticeable increase in the irregularity of her heart as well as in the breathlessness and the signs of congestive heart failure. On May 16, 1929, two days after the onset of the arrhythmia, she showed auricular fibrillation with a ventricular rate averaging over 200 beats per minute. At 10 P.M. on the evening of this day, the patient became extremely restless, there were marked mental changes, pulmonary edema had set in, and at 10:40 P.M. she expired despite all attempts made to control her ventricular rate at that time.

DISCUSSION

The Type of Patients.—All of the patients studied in this series had evidences of organic heart disease for some time prior to the onset of the symptoms and signs associated with premature auricular beats and seizures of paroxysmal auricular fibrillation. The underlying

pathological lesions varied, three showed evidences of chronic rheumatic valvular heart disease, three had hypertension with mild signs of congestive heart failure and one had signs characteristic of multiple myocardial infarction.

Although as has been recently shown by Boas and Weiss¹ with the Cardiotachometer, the sinus rate in normal individuals is usually labile and influenced to a great extent by the extrinsic nerves of the heart, the sinus rates of these patients were particularly susceptible to these influences. They all showed marked diurnal and daily variations of their heart rates even while in bed. Rest in itself or rest in addition to sedative medications such as adequate doses of bromides and chloral and in some instances, morphine sulphate, could not effect the lability of the sinus rate or prevent the appearance of premature auricular beats.

It is very likely that the diseased heart muscle of these patients was a predisposing factor in the initiation of spontaneous premature auricular beats and the increase in sinus rates. For, while excitement, exertion and nervous disturbances were found to induce easily these extra auricular beats reflexly, it is well known that experimentally, direct or indirect stimulation of the cardiac nerves in themselves cannot initiate premature beats. Where premature beats have been demonstrated to follow stimulation of the sympathetic nerves or section of the vagi, they have invariably followed the use of substances known to increase the irritability of the heart.^{2, 3}

The Effects of Digitalis on the Sinus Rate.—The administration of digitalis to these patients during the presence of sinus rhythm slowed the heart from an average rate of 95 beats per minute to 62. The presence and maintenance of a relatively slow sinus rate with normal rhythm were an essential requisite for their welfare; for, as can be gained from the protocols reported above, signs of congestive heart failure were greatest when the heart rate was irregular and rapid even in the presence of premature auricular beats. It was possible to maintain a relatively slow rate and regular rhythm and to prevent the marked lability of the heart rate normally noted, as well as the onset of the premature auricular beats, by the continued use of the drug in doses of 1 to 2 c.c. of the tincture per day.

In this respect these patients form a unique group, for by maintaining a sinus rhythm with a relatively slow rate by the constant use of digitalis from day to day, it was possible in every instance to prevent the onset of irregular heart action. Comfort was evident only in the presence of sinus rhythm, and no other drug could produce this effect except digitalis.

Contrary to general belief, the slowing of the ventricular rate during already established fibrillation was not accompanied by as much benefit even when the rate was as low as 60 beats, for signs of con-

gestive heart failure became increasingly marked even in the presence of the low rate as long as the action of the heart was irregular.

Therefore the use of digitalis during the presence of sinus rhythm may be said to have acted here as a prophylactic drug and prolonged life by preventing the appearance of premature auricular beats and the paroxysms of auricular fibrillation with the severe accompanying signs of congestive heart failure ending at times in rapid death.

No quantitative relationship was observed between the administration of the drug and the changes in the electrocardiograms associated with digitalis administration. A diminution of the T-waves in all three leads with a lowering of the S-T interval below the iso-electric line appeared equally as well after 3 c.c. as after 10 c.c. of digitalis. The persistence of these signs in the electrocardiograms could not be taken as an index of digitalis action, since the disturbances in the sinus rate and rhythm were observed to appear even in the presence of maximum changes in the electrocardiograms usually associated with digitalis and after the drug had been withheld for several weeks. For example, in almost all of the patients the T-waves had not as yet resumed their normal shape when premature auricular beats began to disrupt the sinus rhythm.

The Effects of Digitalis on the Premature Auricular Beats.—Auricular premature beats whether coming singly, in coupled rhythm, or in groups of more at one time, could be easily eliminated in these patients by the effective use of digitalis. Conclusive proof that the administration of the drug was responsible for the abolition of the extra beats is the fact that invariably after their appearance the withholding of the digitalis would result within one to three days in the development of auricular fibrillation with a very rapid ventricular rate. The premature beats would not disappear any faster following the intravenous use of digitalis. Experimental attempts to induce premature auricular beats in these patients and to test out their abolition with digitalis intravenously were unsuccessful. Atropine did not induce premature auricular beats in four patients in whom it was tried in doses of gr. $\frac{1}{20}$ intramuscularly. In one case, however, not only was there an increase in the basic ventricular rate following its use, but showers of premature auricular beats were initiated by the drug within fifteen minutes after its injection, and these were followed by a very rapid irregular ventricular rate with auriculo-ventricular dissociation which lasted for several minutes but disappeared, however, very soon. Such action of atropine has already been observed in man, and the explanation for this phenomenon is based on unequal distribution of the action of the drug on the vagus endings, the fibers supplying the A-V bundle being paralyzed first, thus permitting the escape of the ventricular rhythm and resulting in dissociation of the auricles and ventricles.^{4, 5}

Transitory irregular extrasystolic tachycardia of auricular origin was induced in two of the patients by the use of adrenalin even after digitalis had been used effectively to slow the sinus rate for several weeks. The effects of adrenalin were more marked in the patient in whom it was possible to induce the irregularity of the heart by atropine.

There were increasing symptoms of breathlessness and signs of congestive heart failure following the onset of the premature auricular beats.

In two of the patients in whom bigeminal rhythm had been established after the appearance of auricular extrasystoles, the administration of 6 c.c. of the tincture of digitalis to each one resulted in the abolition of the extrasystoles within four and four and one-half hours respectively.

Their disappearance under the influence of digitalis still remains a fertile field for speculation.

The Effects of Digitalis on Transient Auricular Fibrillation.—In every instance studied it was possible to show a direct relationship between the administration of a single large dose of digitalis and the disappearance of auricular fibrillation, with restoration to normal sinus rhythm following the use of the drug. For the persistence of the unusually high ventricular rate present in all, with which the auricular fibrillation was ushered in, was always accompanied by progressive signs of congestive heart failure, such as extreme breathlessness and hydrothorax, rapid edema of the legs, enlargement of the liver, ascites, and finally pulmonary edema. These events would take place in some patients more rapidly than in others, in the order mentioned beginning shortly after the onset of the arrhythmia and at times reaching alarming proportions within from twenty-four to forty-eight hours. When the pulmonary edema was overwhelming, no medication was of any benefit, and death would take place from asphyxia as was observed at the hospital in two patients. In three patients the irregularity was accompanied by profuse perspiration and symptoms of angina pectoris with radiating pains to the left arm and finger tips which persisted until the ventricular rate receded with the use of the drug.

The disappearance of the irregularity following the use of digitalis and the return to normal of the sinus rate and rhythm were accompanied by a spectacular recovery from the signs of congestive heart failure, all of which would disappear within two or three days after the return of the rhythm to normal.

The ventricular rate was always over 150 beats per minute when the auricular fibrillation set in, and the rhythm during this rapid rate was almost regular at times, exhibiting this regularity even in the electrocardiograms so that to one not accustomed to seeing these cases, a diagnosis of the tachycardia was difficult.

In one case that was followed constantly, both during the day and night, the administration of a single large dose of digitalis halved the ventricular rate of 210 within four hours after the medication was given orally, and within two hours when it was given intravenously at another time. This low rate of about 100 beats lasted for two days and then gradually came down to about the relative normal of 60 to 70 beats per minute when the transition to sinus rhythm took place as revealed by the electrocardiograms.

In several cases in which the digitalis was given orally in doses of 3 c.c. per day after the establishment of the auricular fibrillation the ventricular rate would also slow down but not until from 15 to 21 c.c. of the tincture had been administered. If further use of the drug was made, partial heart-block with a rate of 45 beats and premature beats of the ventricle with bigeminal rhythm due to them would set in, indicating the toxic action of digitalis. By withholding digitalis at such times there would be a gradual return of the rate to a level of from 60 to 70 beats per minute and then sinus rhythm would be established shortly afterward. The signs of congestive heart failure did not disappear as readily when small doses of digitalis were used to slow the ventricular rate.

Following the use of a single large dose of digitalis and the restoration of sinus rhythm, the onset of auricular fibrillation could always be prevented by maintaining a relatively low sinus rate with the constant use of daily doses of digitalis of from 1 to 3 c.c.

The transient nature of auricular fibrillation in patients with heart disease is now too well appreciated to require detailed comment. Its evanescent appearance and disappearance with only slight discomfort have been observed in certain patients over a period of years without adding to the seriousness of their prognosis. In many instances the subjects of these seizures were not even aware of anything being wrong with their cardiac mechanism. Consequently the benefits of the administration of any drug during these seizures in the absence of symptoms and signs is questionable.

In such patients, quinidine has, nevertheless, been found of unusual value not only in curing the arrhythmias but also in preventing them. Quinidine is, however, contraindicated in congestive heart failure judging from the unusually large series of deaths following its use at the Montefiore Hospital. It is therefore gratifying to learn that the administration of digitalis in single large doses given at one time may abolish auricular fibrillation with a very rapid ventricular rate in patients with the particular type of irregularity reported in this study.

The action of digitalis on the auricles being as complex as it is, no attempt is made to explain the restoration of sinus rhythm following the administration of the drug in these cases.

SUMMARY

Seven patients with organic heart disease are reported who were subject to recurrent attacks of auricular fibrillation with a very rapid and persistently high ventricular rate that did not slow with rest. In each instance this arrhythmia was preceded for several days by premature auricular beats, first coming on singly, then in groups of two or more at a time.

In most instances the premature auricular beats were easily induced by psychic, nervous or emotional disturbances. If they were allowed to continue, auricular fibrillation invariably developed after two or three days. The premature auricular beats could be abolished and the onset of the auricular fibrillation could be prevented by the administration of adequate doses of digitalis, either orally or intravenously.

The onset of these irregularities was always associated with progressive signs of congestive heart failure, such as extreme breathlessness, rapid enlargement of the liver, effusion in the serous cavities and pulmonary edema.

A large single dose of digitalis administered during the presence of an attack of auricular fibrillation resulted in the slowing of the heart rate within four to five hours when the drug was given orally, or within two hours when it was given intravenously. Restoration to sinus rhythm would not take place, however, until from two to three days after the administration of digitalis. All the signs and symptoms of congestive heart failure precipitated by the disturbances in rhythm would gradually pass away in the presence of sinus rhythm.

The administration of small daily doses of digitalis during the presence of auricular fibrillation, in several patients in whom this form of therapy was attempted, slowed the heart rate but did not abolish the arrhythmia or relieve the symptoms and signs.

Six of these patients were ambulatory and could carry on their daily restricted activities so long as sinus rhythm was present. A relatively normal sinus rate could be maintained in all by the use of digitalis in small daily doses during the presence of sinus rhythm. If the drug was discontinued for any length of time even when sinus rhythm was present, the premature auricular beats would reappear and be followed by auricular fibrillation with a very rapid ventricular rate. If the ventricular rate could not be controlled with digitalis, death would take place within a short time from asphyxia due to pulmonary edema.

Because of the unusual response of these patients to variable doses of digitalis in the presence of sinus rhythm as well as of auricular premature beats and auricular fibrillation, they form a distinct group among patients with heart disease and should be given special consideration when encountered in practice.

REFERENCES

1. Boas, E. P., and Weiss, M. M.: The Heart Rate During Sleep as Determined by Cardiotachometer: Its Clinical Significance, *J. A. M. A.* 92: 2162, 1929.
2. Levy, A. G.: Further Remarks on Ventricular Extrasystoles and Fibrillation Under Chloroform. *Heart* 7: 105, 1918.
3. Rothberger, C. W., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikularen Tachykardie durch Acceleransreizung. *Arch. f. d. ges. Physiol.* 142: 461, 1911.
4. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropin. *Arch. Int. Med.* 16: 989, 1915.
5. White, P. D.: Ventricular Escape. *Arch. Int. Med.* 18: 244, 1916.

THE SIGNIFICANCE OF SPLINTERING OF THE TERMINAL PORTION OF THE QRS DEFLECTION OF THE ELECTROCARDIOGRAM*

LEONARD STEUER, M.D., AND HAROLD FEIL, M.D.
CLEVELAND, OHIO

CONSIDERABLE diagnostic importance has been attached to splintering or notching of various portions of the QRS complex. Such notching is usually associated with other electrocardiographic changes which render the records distinctly abnormal. A large bizarre QRS complex, notched, with a duration in excess of 0.1 second and T in the opposite direction completes the picture of a bundle-branch lesion. A notched QRS complex in all leads, low in voltage, is evidence of intraventricular block. In this study, however, we wish to limit ourselves to a discussion of splintering of the final deflection of the QRS complex as an isolated electrocardiographic phenomenon, and to point out the significance of such splintering.

A. M. Wedd¹ has already called attention to the significance of notching of the R-wave and states that this is frequently encountered in cases of unquestioned myocarditis. In Wedd's series of thirty cases, seventeen showed notching of R in Lead III alone; three showed the notching in all leads; four in Leads I and III; three in Leads II and III; two in Leads I and II; and one in Lead I alone. Although we agree that notching of the R in one or two leads may be of clinical significance we must admit that similar notching does occur in records of normal individuals.

The appearance of such notching in normal individuals has been pointed out by Lewis and Gilder.² In a study of fifty normal individuals they found notching of R₁ in three instances; of R₂ in one instance; of R₃ in six instances in which its identification was not complicated. They likewise found splintering of the S-wave in two instances in Lead II, and noted that apart from eleven cases of splintering in the opening events of ventricular systole, a division of S was never seen in Lead III. Wiggers³ states that humping, notching or splintering of the R-wave is normal when it occurs on a small wave in a single lead, and when it occurs near the base of the ascending or descending limbs of two different leads.

In an effort to check the frequency with which splintering of the terminal part of the QRS deflection occurred in our series of normal records we examined the electrocardiograms of 119 known normal

*From the Medical Clinic and Electrocardiographic Laboratory of Mt. Sinai Hospital of Cleveland.

individuals. Such notching occurred in one or two leads in twenty-one cases of this series. It appeared in Lead I in five instances; in Lead II in eight instances; in Lead III in two instances; in Leads I and III in two instances; in Leads I and II in one instance; in Leads II and III in three instances. It is evident, however, that in the total of 119 normal individuals studied, in no instance did notching of the final part of the QRS complex occur in all three leads.

On the other hand, in a series of 4000 electrocardiograms taken from the files of Mt. Sinai Hospital we found splintering of the final part of the QRS deflection in all leads as the only electrocardiographic abnormality in 34 instances. In all cases where splintering occurred in three leads there was unquestionable clinical evidence of cardiac abnormality. The types of clinical cardiac abnormalities represented in these cases are as follows:

| | | |
|---------------------------|----------|-------------|
| Hypertension | 14 cases | 41 per cent |
| Rheumatic heart disease | 13 cases | 38 per cent |
| Coronary arteriosclerosis | 5 cases | 15 per cent |
| Hyperthyroidism | 1 case | 3 per cent |
| Developmental defect | 1 case | 3 per cent |

In these records with notching in all leads left preponderance occurred in 22 instances (65 per cent); right preponderance in 2 instances (6 per cent); no preponderance in 10 instances (29 per cent).

The actual cause of this splintering is a matter of speculation at present. We know that the QRS group of deflections corresponds to the excitation of the ventricles and that the conus and base of the left ventricle become electrically active at the peak of the R or a little later.⁴ The terminal phase of the QRS complex is completed with excitation of both ventricles, and it is not unreasonable to assume that the notching is associated with an abnormality in the Purkinje conduction. This may be due to myocardial enlargement or endocardial changes—either of which might cause changes in the record of the course of excitation.

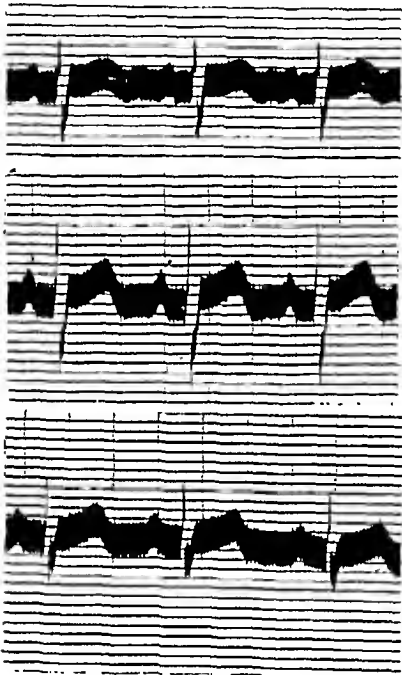
SUMMARY

A series of 119 electrocardiograms of 119 normal individuals has been studied and notching in the terminal portion of the QRS complex in all three leads has not been found in any of the cases. Thirty-four cases showing the presence of such notching in all leads have been studied, and it has been found that there is distinct evidence of cardiac abnormality in all instances. It is therefore concluded that an electrocardiogram which shows splintering in the terminal part of the QRS complex in all leads is distinctly abnormal. This finding has been present in various types of cardiac disease. Illustrative cases and records are shown.

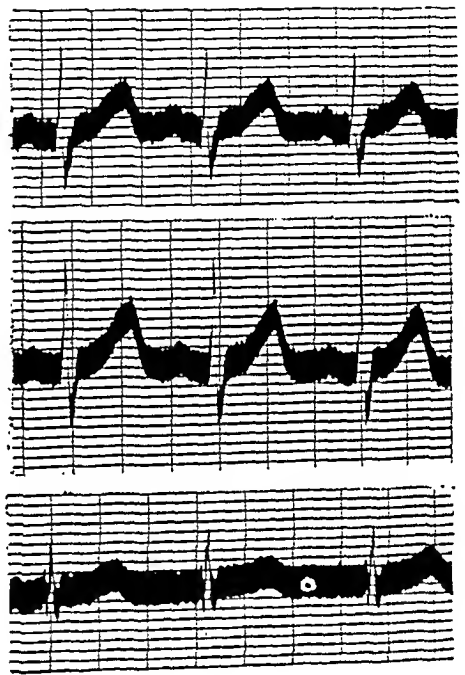
ILLUSTRATIVE CASES

CASE 1.—E. C. A white male of 8 years. Rheumatic fever at 5 years. Systolic and diastolic murmurs at apex. Orthodiagram shows straightening of middle left cardiac margin with elongation of the shadow of the left ventricle. Clinical Diagnosis: Rheumatic heart disease, mitral stenosis and insufficiency with normal exercise tolerance.

CASE 2.—D. K. A white female of 19 months. Not a blue baby. Pneumonia at age of 7 months. Musical systolic murmur, best heard along left sternal margin in second and third intercostal spaces. Also heard at apex. Orthodiagram shows definite mitral configuration with straightening of the middle left cardiac margin. Considerable bulkiness to right and left suggesting a congenital septal defect. Chest 16 cm. Transverse diameter of heart 8 cm. Clinical Diagnosis: Developmental defect.



Case 1.

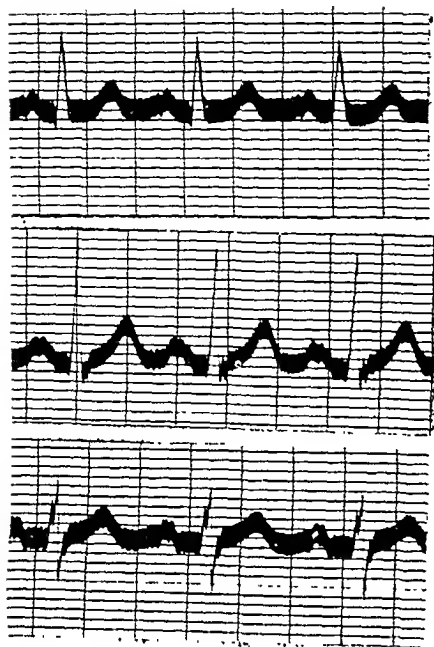


Case 2.

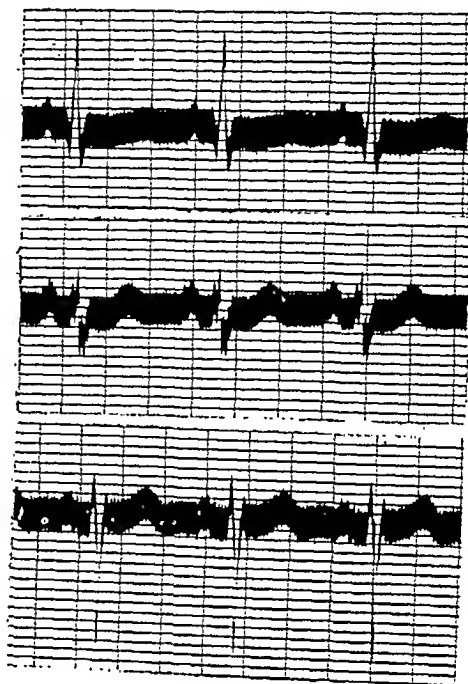
CASE 3.—F. D. White female of 16 years. Attacks of chorea at 7 years and 13 years. Loud systolic murmur at apex. Left border of cardiac dullness 10 cm. from midsternal line in fifth interspace. Orthodiagram shows mitral configuration with bulging of upper left cardiac margin and additional enlargement to right and left. Bulging of left auricle in right lateral position. Chest 23 cm. Aorta 3.5 cm. Transverse 13.5 cm. Clinical Diagnosis: Mitral insufficiency.

CASE 4.—N. G. White female of 62 years. Admitted to hospital in shock two days after severe pectoral pain. Diagnosis of coronary occlusion by one of writers. Notching appeared as first sign of abnormality in electrocardiogram. Later electrocardiographic signs of coronary occlusion appeared. Clinical Diagnosis: Coronary sclerosis with occlusion of coronary artery.

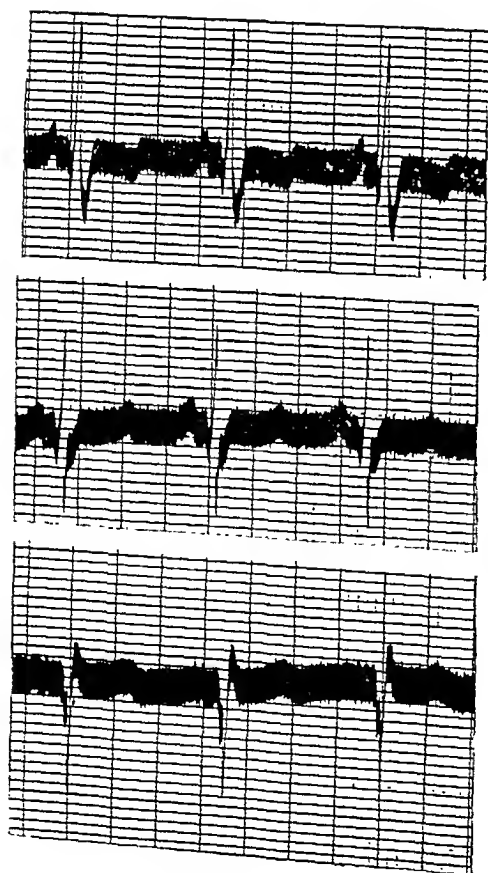
CASE 5.—M. G. White female of 69 years complaining of precordial pain. Increased palpable precordial activity. Right border of cardiac dullness 1 cm. to right of sternum. Left border of cardiac dullness 2 cm. to left of midclavicular line in fifth interspace. Harsh systolic murmur over entire precordium. Blood



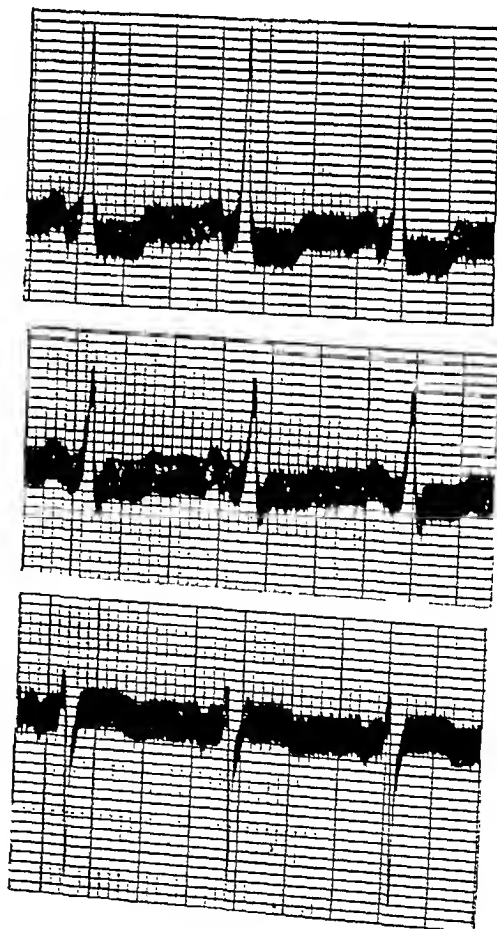
Case 3.



Case 4.



Case 5.

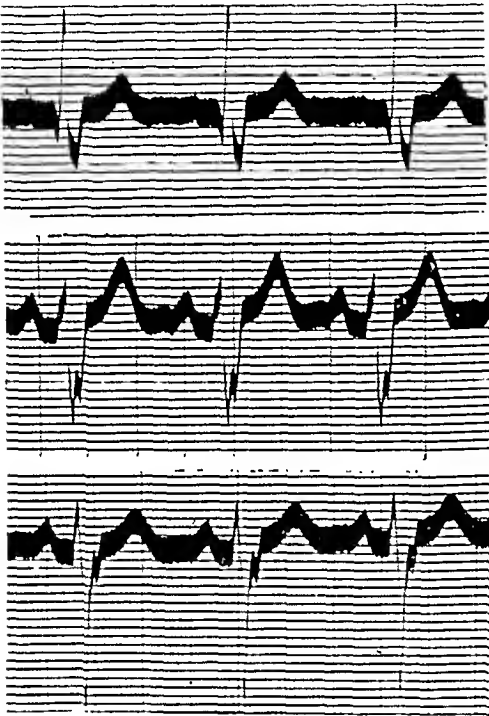


Case 6.

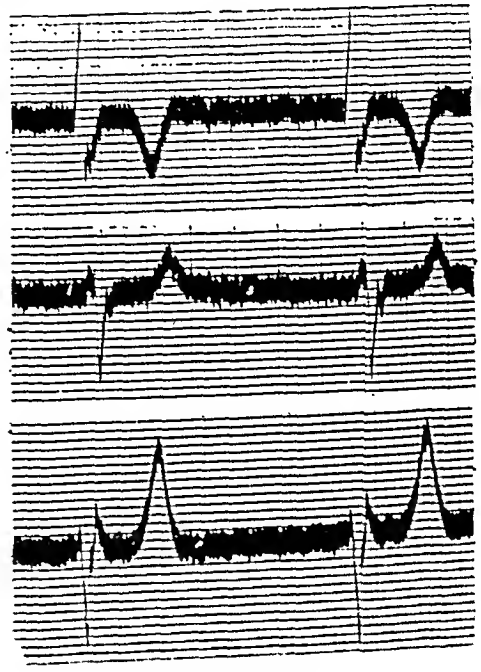
pressure 210/120; 178/86; 190/110; 160/76. Clinical Diagnosis: Hypertension with cardiac hypertrophy.

The following autopsied cases are presented. These show the splintering of the terminal portion of the QRS deflection in the presence of other electrocardiographic abnormalities.

CASE 6.—L. W. A white female of 60 years admitted to the hospital complaining of shortness of breath and high blood pressure of two years' duration. Has taken antiluetic treatment for the past seven years and malaria treatment for general paresis three years ago. Presented picture of congestive heart failure with enlargement of the left ventricle. A faint diastolic murmur was heard at the aortic area. Blood pressure 240/90; 200/90; 190/90. Changed from normal mechanism to auricular fibrillation during hospital stay and went downhill rapidly. No digitalis had been administered at time of first electrocardiogram. Orthodia-



Case 7.



Case 8.

gram shows tremendous enlargement to the left with considerable diffuse dilatation and marked increased density of the aorta. Chest 26 cm. Transverse 16 cm. Aorta 9 cm. Clinical Diagnosis: Hypertension with cardiac hypertrophy, luetic aortitis with insufficiency.

Anatomical Diagnosis: Hypertrophy and dilatation of the heart (chiefly left ventricle); (Heart weight 800 grams); luetic mesaortitis with involvement of the leaflets and slight insufficiency; generalized arterial and arteriolar sclerosis.

CASE 7.—M. N. A white male of 56 years admitted complaining of fainting spells of six months' duration. Patient presented the large head and bowing of the long bones typical of Paget's disease. Modern enlargement of the left ventricle with a musical systolic murmur at the apex. Blood pressure 176/80. During fainting spells heart mechanism would change from normal to block. Developed congestive failure and expired. Orthodiagram showed enlargement of heart to left.

Clinical Diagnosis: Generalized arteriosclerosis; heart-block; congestive heart failure; Paget's disease. Anatomical Diagnosis: Calcium deposits mitral and aortic

valves involving conduction system; mitral stenosis, considerable; aortic stenosis, moderate; hypertrophy of myocardium, weight 460 grams.

CASE 8.—N. A. White male of 71 years admitted because of fractured skull. Heart enlarged, arrhythmic, no murmurs. Became stuporous, cyanotic and expired. Clinical Diagnosis: Fractured skull, auricular fibrillation. Anatomical Diagnosis: Fractured skull; cardiac hypertrophy and dilatation, weight 550 grams; moderate atherosclerosis of coronary arteries with several areas of scarring in myocardium.

REFERENCES

1. Wedd, A. M.: Arch. Int. Med. 25: 515, 1919.
2. Lewis, T., and Gilder, M. D. D.: Phil. Tr. Roy. Soc. London 202: 351, 1912.
3. Wiggers, Carl J.: Principles and Practice of Electrocardiography, St. Louis, 1929, p. 102, The C. V. Mosby Company.
4. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, 1925, p. 95, Paul B. Hoeber, New York.

SINO-AURICULAR BLOCK*

A. W. WALLACE, M.D., AND L. N. KATZ, M.D.
CLEVELAND, OHIO

SINO-AURICULAR block is a rather rare form of cardiac arrhythmia. The condition was first described by Wenckebach¹ in 1907, and a comprehensive review is given by Levine² of fourteen cases published before 1916. Levine, in his review, adds four cases of his own. Barlow³ reviews thirty-two cases which had appeared in the literature from 1916 to 1926 and also adds four cases. White and Viko⁴ reported only eleven cases in 3219 electrocardiograms taken at the Massachusetts General Hospital from 1914 to 1922. The condition, however, is probably more common than is suspected (Levine,² Smith,⁵ White⁶).

The most common form of the abnormality is that of an occasional dropped beat. It is unusual to find two or more beats dropped out in succession. Levine² reports one such case where five beats were dropped out, and in the series reported by Barlow no mention was made of any such case. Although delayed A-V conduction is quite frequently associated with S-A block, and is emphasized by Lewis⁷ who says that it is too frequent to be accidental, it is rare to have conduction so impaired that a ventricular beat is dropped.

A case of S-A block with one and two dropped beats and delayed A-V conduction with a dropped ventricular beat is here reported.

CASE REPORT

Miss L. S., aged 30 years, a stenographer, entered the hospital September 9, 1929, complaining of shortness of breath, palpitation, and edema of the lower extremities. About three years before, the patient had had an attack of influenza, and about two months following this she noticed that on slight exertion she would become short of breath. This was her first intimation of any heart trouble. Since then her activities had been greatly restricted because any overexertion caused shortness of breath and decompensation. The patient had had chorea twice, at the ages of 5 and 9 years, and had had many sore throats before her tonsils were removed in 1922.

Physical examination on admission showed a slightly undernourished female. The heart was slightly enlarged to the left and right, and there were a systolic thrill and diastolic shock palpable over the precordium. A late diastolic and systolic murmur were heard along the left sternal border, with an accentuated pulmonic second. The rhythm was regular, and the blood pressure was 100/68 mm. There were scattered râles at both bases, and there was slight pitting edema over both lower extremities. The white blood count was 10,200; the erythrocytes, 4,210,000; hemoglobin, 75 per cent (Sahli), and the urine was negative. Digitalis folia, gr. 3 daily, was given the patient and, with rest in bed, cardiac decompensation disappeared, and the patient was discharged much improved September 10, 1929.

*From the Heart Station, St. Luke's Hospital, Cleveland, Ohio.

The patient was readmitted to the hospital October 12, 1929, because of cough and sore throat. After four days' rest in bed and local treatment for an acute nasopharyngitis she was greatly improved and left the hospital against advice. She returned three days later (October 19) with bronchitis and remained in the hospital until October 24, 1929. During this stay, she showed no signs of decompensation.

On January 27, 1930, the patient was readmitted to the hospital. One week before, she had had an attack of "influenza" followed in three days by painful joints. Examination at this time showed a liver which was just palpable and somewhat tender. The heart was the same as on previous examinations. There were tenderness and swelling of the right elbow and left ankle. The patient was put on salicylates and digitalis folia, gr. 1 b.i.d. The arthritis did not spread and the

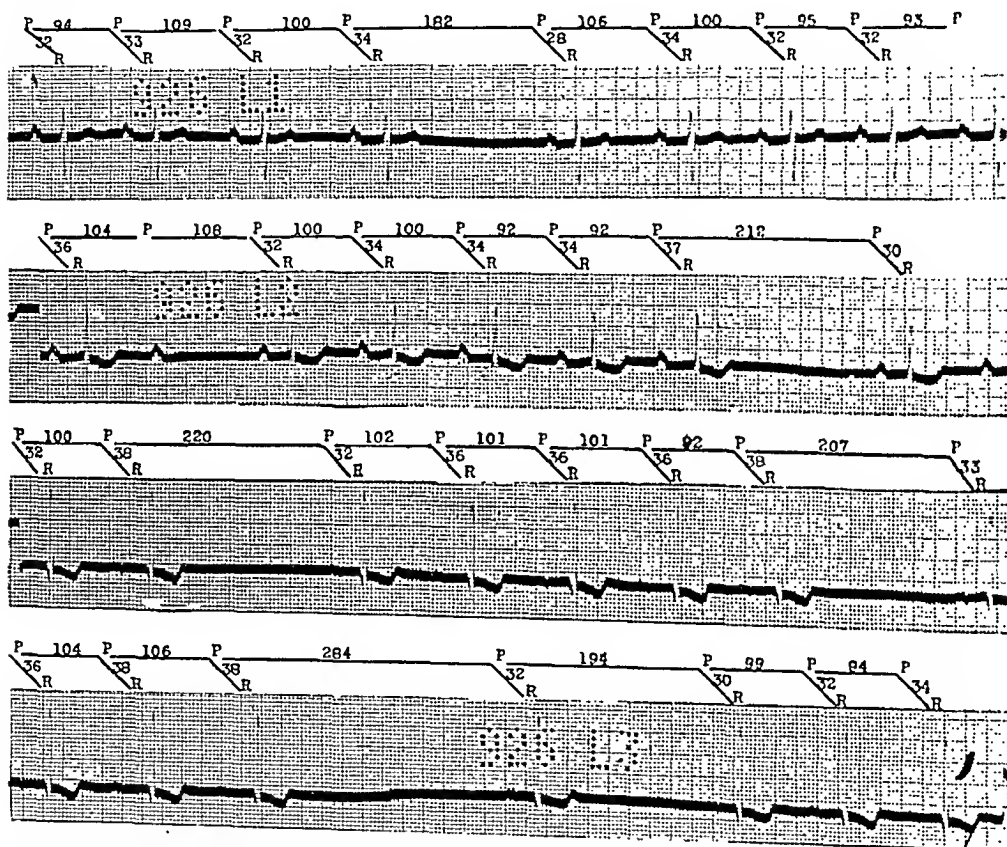


Fig. 1.—Electrocardiogram taken on February 19, 1930. Top strip, Lead I; next strip, Lead II; two lower strips are from Lead III. Above each strip is plotted the P-P and P-R intervals.

patient improved. On February 7, 1930, an irregularity of the pulse was noticed for the first time. The patient was conscious of this irregularity and said that her heart was "skipping beats." An electrocardiogram was taken which showed sinoauricular block. The patient insisted on leaving the hospital the next day against advice and was told to stop the digitalis which she had been taking more or less constantly since her first admission to the hospital.

On February 18, 1930, the patient was admitted at 9:30 P.M. Since her discharge ten days before she had been taking digitalis "occasionally." The day before admission she had developed frequency and pain on urination. Examination at this time showed the liver very tender and down to the umbilicus. The left elbow was painful and swollen. There was marked edema of both lower extremities. The heart showed a cardiac irregularity similar to the one of February 7, the regular

rhythm being interrupted by a dropping of one or two beats. The urine showed one plus albumin and many white cells. An electrocardiogram taken the next morning (Fig. 1) showed sino-auricular block. Atropine sulphate, gr. 1/75, was injected subcutaneously, and twenty minutes later another electrocardiogram was taken (Fig. 2) which showed complete disappearance of the S-A block with a quickening of the rate. The urine gradually cleared, the edema disappeared, and the patient was once more made comfortable. The heart was regular and no evidence of S-A block was ever noted after the atropine had abolished it. The patient was discharged on March 8, 1930, and has not been heard from since.

DISCUSSION OF ELECTROCARDIOGRAMS

In Figs. 1 and 2, the electrocardiograms taken on February 19 are shown. The record obtained on February 7 resembles Fig. 1 in prac-

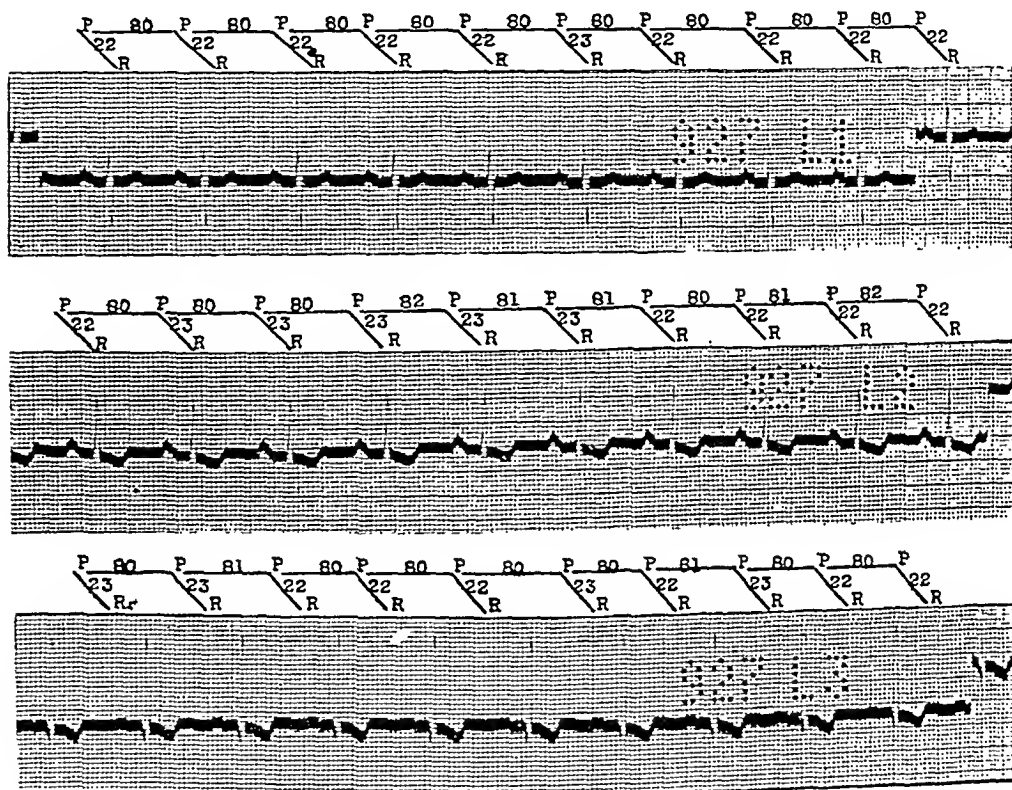


Fig. 2.—Electrocardiogram taken on February 19, 1930, twenty minutes after the administration of the one-seventy-fifth of a grain of atropine sulphate.

tically all respects except that no dropped ventricular beat was found. Above each curve in Figs. 1 and 2, are plotted the P-P and P-R intervals in hundredths of a second for ready reference. There is present in Fig. 1 a right ventricular preponderance as indicated by the inversion of the QRS in Lead I. There is some slurring of the R in Lead II. The P-wave is notched in all three leads, and a typical digitalis inversion of the T-wave is seen in Leads II and III. The P-R interval is prolonged, ranging from 0.32 to 0.38 of a second, and in Lead II there is a dropped ventricular beat. A sinus arrhythmia is present, and occasionally a long pause occurs which is equal to two

or three times the average cycle. Thus in Lead I the fourth P-P interval is equivalent to twice 0.91 of a second; in Lead II the fifth P-P interval is equivalent to twice 1.06 of a second; the long pauses in the two strips of Lead III are equivalent to twice 1.10 of a second, twice 1.035 of a second, thrice 0.913 of a second and twice 0.97 of a second, respectively. These figures are well within the variation present in the shorter P-P intervals, which vary from 0.92 to 1.09 of a second. Therefore, there can be little doubt that the longer pauses are due to so-called sino-auricular block. The longer pauses in the electrocardiogram taken on February 7 were also multiples of the shorter cycles, i.e., the longer P-P intervals were twice 0.89 of a second, twice 0.825 of a second, thrice 0.907 of a second, twice 0.89 of a second, twice 0.885 of a second, twice 0.94 of a second, twice 0.885 of a second and twice 0.90 of a second respectively. These values are within the range of the shorter P-P intervals, namely from 0.80 to 1.00 of a second. These observations indicate the presence of sino-auricular block in this record also.

It is interesting to observe that following the long pauses, the P-R interval shortens for one or two cycles, just as it does when a ventricular complex is dropped out (Fig. 1). Unlike the cases reported by Levine,² when two pauses come together in this case, the second is shorter (Fig. 1, last strip).

An attempt was made to evaluate the rôle played by the vagi by giving the patient one seventy-fifth of a grain of atropine sulphate after Fig. 1 was taken. A record twenty minutes later (Fig. 2) showed a complete disappearance of the sino-auricular block, together with the sinus arrhythmia. At the same time the P-P and P-R intervals shortened somewhat. However, the configuration of the complexes of the electrocardiogram remained essentially unchanged. This effect of atropine would indicate that the sino-auricular block was caused by a vagal effect probably as a result of the action of digitalis. Since the sino-auricular block—so-called—was associated with a delayed conduction in the A-V node and since both were alleviated by atropine, it would appear that the change in the sinus node in this case is in the nature of a conduction disturbance rather than of absence of impulse initiation.

SUMMARY

A case is presented which shows sino-auricular block with single and double dropped beats, associated with a prolonged A-V conduction and an occasional dropped ventricular beat. The sino-auricular block was relieved and the A-V conduction improved by atropine indicating that the sino-auricular block was a vagal effect presumably due to digitalis.

REFERENCES

1. Wenckebach, K. F.: Arch. f. Anat. u. Path., Physiol. Abt., 297, 1906; Die Unregelmässige Herztätigkeit, Leipzig, 1914, W. Engelmann.
2. Levine, S. A.: Arch. Int. Med. 17: 153, 1916.
3. Barlow, P.: Lancet 212: 65, 1927.
4. White, P. D., and Viko, L. E.: Am. J. M. Sc. 165: 659, 1923.
5. Smith, P.: Am. J. M. Sc. 162: 575, 1921.
6. White, P. D.: Arch. Int. Med. 25: 420, 1920.
7. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, 1924, ed. 3, p. 411, Shaw and Sons, London.

THE MYOCARDIUM IN YELLOW FEVER

I. THE MYOCARDIAL FUNCTION IN EXPERIMENTAL YELLOW FEVER*

WRAY LLOYD
TORONTO, ONT.

INTRODUCTION

AMONG the changes in myocardial function occurring during the course of yellow fever, bradycardia has been noted most frequently by clinical observers. Although Delmas¹⁴ in his treatise on yellow fever published in 1822 described this phenomenon, it remained for Charles Faget²⁰ to study accurately and to chart its behavior. He promulgated the law of a slowing heartbeat with a rising temperature in the early days of yellow fever, so that this seeming paradox became known as Faget's sign. It was confirmed by his confrere Tonatre⁶² and by later observers.^{56, 12, 57, 5, 30, 21, 44, 43} Retardation of the heart rate in yellow fever has also been recorded with considerable constancy by most recent workers in this field. It has been described by Noguchi⁴⁸ and by Elliott¹⁹ as existing in cases of the disease met with in Guayaquil, Ecuador, in 1918. Selwyn-Clarke⁵⁸ and Aitken,^{1, 2, 3} as well as Mahaffy, Walcott, and Klotz,²⁸ observed the sign during the course of the disease in British West Africa in the years 1925 and 1926. The existence of this finding in the yellow fever of Senegal has been reported by Lasnet,²⁹ a French contemporary of these observers.

Investigation of the type and causation of the bradycardia occurring in yellow fever has been the basis of the experiments of several workers. In 1921 Cohn and Noguchi¹⁰ first attempted to record and differentiate the type of bradycardia in experimental animals with the aid of electrocardiography. Unfortunately their results upon monkeys and guinea pigs inoculated with *Leptospira icteroides* and *Leptospira icterohaemorrhagiae*, in the light of our present knowledge, must be related to the functional pathology of Weil's disease rather than to that of yellow fever. Cannell,⁶ in 1928, pointed out that bradycardia occurred in this disease independently of jaundice. The same author noted fatty degeneration in the auriculo-ventricular bundle and suggested that the occurrence of auriculo-ventricular dissociation might offer a possible explanation of the slow pulse rate in the disease. During the epidemic of yellow fever in Rio de Janeiro in 1928, Chagas⁸ described a clinical picture occurring in from 10 to 15 per cent of his

*These studies have been performed under the tenure of a grant from the Banting Research Foundation. Their accomplishment has been possible because of the facilities made available in the Yellow Fever Laboratory of the International Health Division of the Rockefeller Foundation, at the Rockefeller Institute for Medical Research, and in the Physiological Laboratory of the Hospital of the Rockefeller Institute. The author is greatly indebted to the courtesy shown him by the directors of these laboratories, Dr. W. A. Sawyer and Dr. A. E. Cohn. During the absence of Dr. Cohn, Dr. H. J. Stewart kindly provided necessary facilities for the work.

From the Department of Pathology and Bacteriology of the University of Toronto.

patients, more frequently among those who recovered, which he termed a suprarenal syndrome of the disease. The symptoms which this observer ascribed to an adrenal origin were profound debility, peripheral vasodilatation with redness of the face, dermographism, frequent capillary hemorrhages, arterial hypotension, bradycardia, and less often dissociation of cardiac rhythm. The following year Chagas and de Freitas,⁹ in electrocardiographic studies of human cases, reported the occurrence of bradycardia and rarely of auriculo-ventricular dissociation. This latter phenomenon was assumed to be due to the influence of the vagosympathetic system.

TECHNICAL METHODS

Graphic Methods of Investigation.—A series of twenty animals was employed, of which seventeen belonged to the species *Macacus rhesus* and three to the species *Macacus cynomolgus*. Electrocardiographic tracings were taken of the cardiac action in these animals before inoculation with yellow fever virus. After a period varying from one hour to forty-eight hours after the registration of the normal electrocardiograms for each monkey, the animal was inoculated intraperitoneally or subcutaneously with 0.5 c.c. of fresh infectious monkey blood (Asibi virus) withdrawn by cardiac puncture from an infected animal on the first day of fever. Upon frequent occasions, when virus in this form was not available, a quantity of desiccated blood, the preserved form of the Asibi virus,⁵⁵ equivalent to 0.5 c.c. of whole blood, was dissolved in Loekke's solution and used for the inoculation. Electrocardiograms were obtained whenever possible upon these animals during the period of incubation, and upon successive days of the disease. Frequently during the latter days of the illness tracings were taken twice daily.

The monkeys were anesthetized in each instance five minutes before being electrocardiographed. In securing electrocardiograms upon the first four animals, sodium iso-amyl-ethyl barbiturate, administered in solution intraperitoneally, was used as an anesthetic. Since in these earlier experiments it was observed that, with the daily employment of this anesthetic, the experimental animals died at the end of a period of time twenty-four to forty-eight hours shorter than the average duration of illness in the monkey inoculated with Asibi virus, and before the development of well-marked yellow fever lesions in the viscera, it was abandoned to be replaced by ether. The dosage of the former drug used to produce anesthesia in an animal amounted to 0.05 gram per kilogram of body weight. All electrocardiograms were taken with the animals in a supine position with four points of the skeleton, the two scapular spines and the two ischial tuberosities, in the same horizontal plane.

The electrocardiograms were recorded from the three standard leads. In this place it may be noted that Lewis³⁵ found no conspicuous differences between the levo- and dextrocardiograms in man and monkey. One animal, a *Macacus cynomolgus* which developed peritonitis during the course of the experiments, was subjected to electrocardiography on successive days of the disease preceding death. The electrocardiograms on this monkey, which did not receive yellow fever virus, are offered as controls. In all, 256 tracings were obtained upon this series. Of 19 animals inoculated with the virus, 17 died of yellow fever, while 2 recovered from the disease. Following the completion of each physiological experiment and the death of the animal, a post-mortem examination was made. The heart was removed, and its cavities were opened in such a manner as to preserve intact the sino-auricular node and the auriculo-ventricular bundle. The whole cardiac tissue was then fixed in Zenker's fluid. Sections were also taken of the liver, kidney, and spleen in each case for the purpose of verifying microscopically the existence of yellow fever lesions in these organs.

Surgical Methods of Investigation.—The hypothesis of vagus nerve stimulation as the cause of bradycardia, suggested by some writers,³ obviously necessitated investigation. Two monkeys were obtained at death, and dissections were made of the cervical and thoracic portions of the vagus nerve in order to obtain a familiarity with its course and distribution in *Macacus rhesus*. Ten animals were then selected for the elucidation of the problem. Six of these monkeys had been infected with yellow fever virus and formed a group of a larger series in which the development of slow heart action had been noted. Electrocardiograms designed to record the existing bradycardia were taken on these animals before submitting them to the operation of bilateral vagus section. In one experiment electrocardiograms were recorded after the vagi had been isolated and were about to be cut. In all experiments vagus section was performed immediately after the preliminary recording of the electrical changes accompanying the heartbeat. Electrocardiograms were taken again directly after the vagus section operation, and frequently additional ones were obtained from ten to fifteen minutes later. The remaining four animals of the group of ten monkeys relegated to the study of the problem of vagus effects were monkeys in apparent health upon whom vagus section was performed for purposes of control. In this series as well, tracings were taken immediately antecedent and subsequent to vagus section. Both the surgical and electrocardiographic procedures were carried out under ether anesthesia. After the completion of each vagotomy experiment the animal was killed by the continued administration of ether.

The operation of vagus section was performed first on the right vagus nerve and then on the left. Section of the nerve was carried out at the point where the superior belly of the omohyoid muscle crossed the common carotid artery. In man, most of the rami cardiaci superiores arise from the vagus trunk below this level, while all the rami cardiaci inferiores arise either from the right vagus and recurrent laryngeal nerves or the left recurrent laryngeal nerve below this point.

However, this method of bilateral vagus section would not insure the cutting of those few fibers which may sometimes arise from the superior laryngeal nerve. I am unable to say whether such fibers exist in *Macacus rhesus*. The method of abrogating vagus function by section of the two main trunks was chosen in preference to the more usual one of atropinization, because it would seem to offer more certain and less controvertible results.

Following the completion of these physiological experiments, autopsies were performed upon the animals. The hearts were carefully excised from the bodies, so as to include the muscle at the junction of the superior vena cava with the right auricle. After removal of each heart, its cavities were opened, and the entire cardiac tissue was fixed in Zenker's fluid.

RESULTS

1. *Physiological observations upon the sino-atrial node and vagus nerve.*

The observations upon the cardiac rate demonstrated that bradycardia is a constant finding in experimental yellow fever in the monkey. It was absent in only one instance, that of *M. rhesus* 15, in which cardiac puncture and the attendant deprivation of blood had been instrumental in producing the early death of the animal. In *M. rhesus* 8, there existed normally a very slow heart rate. The rate increased markedly on the third day of the incubation period, after which it became retarded and continued so during the further course of the disease. The bradycardia was found to be for the most part a progressive one, the heart rate diminishing from day to day of the disease and even from morning to afternoon of the same day. Occasionally the

TABLE I
HEART RATE OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS

| MONKEY NUMBER | NORMAL RATE | DAYS OF INCUBATION | | | FIRST DAY FEVER | | SECOND DAY DISEASE | | THIRD DAY DISEASE | | FOURTH DAY DISEASE | | FIFTH DAY DISEASE | | RECOVERY PERIOD |
|------------------|----------------|-----------------------|---|-----|--------------------|------|-----------------------|------|----------------------|------|-----------------------|------|----------------------|------|--------------------|
| | | 1 | 2 | 3 | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | |
| 1 | 189 | | | 3 | | 177 | 205 | 186 | D | | 150 | D | | | |
| 2 | 208 | | | | | | 160 | 118 | 212 | | | | | | |
| 3 | 188 | | | | | 216 | 189 | | D | | | | | | |
| 4 | 250 | | | | 216 | | 182 | D | 204 | | | | | | |
| 5 | 202 | | | 167 | 177 | | 233 | | 197 | 180 | D | | | | |
| 6 | 217 | | | | 270 | | 215 | | 186 | | 153 | | 180 | | |
| 7 | 200 | | | 223 | 186 | | 170 | | | | | | | | 211 |
| 8 | 160 | | | | | | 193 | | 162 | D | | | | | |
| 9 | | 213 | | | | | 218 | | 197 | 147 | | | | | |
| 10 | 210 | | | | | | | | 160 | | D | | | | |
| 11 | 223 | | | | | | | | 168 | | 152 | | | | 191 |
| 12 | 205 | | | | | | | | | | 80 | D | | | |
| 13 | 191 | | | | | | | | D | | | | | | |
| 14 | 213 | | | | | | | 173 | 173 | 144 | | | | | |
| 15 | 221 | | | | | 230* | D | | | | | | | | |
| 16 | 232 | | | | | | | | 174 | D | | | | | |
| 17 | 226 | | | | | | | | 34† | D | | | | | |
| 18 | 228 | | | | | | 204 | | 150 | D | | | | | |
| 19 | | 226 | | | | | | | 162 | D | | | | | |
| 20 | 171 | | | | | 228 | 222 | 186 | D | | | | | | |
| Control | | | | | | | | | | | | | | | |

*Bled from heart, animal died.
†Animal died during inscription of Lead III.
D—Animal dead.

rate was rapid during the early days of the fever, but it was never accelerated in the end stages. When recovery took place, the heart rate regained its normal frequency. Bradycardia was absent in the severe infection of the peritoneum which killed the previously mentioned *M. cynomolgus* after a period equal to the average length of illness of monkeys dying as a result of infection with the Asibi virus.

It was characteristic of the course of experimental yellow fever in this series of animals that the heartbeat remained regular in its occurrence. Only twice was disturbance of rhythm met with during the course of the disease. An irregular cardiac function was observed in the dying heart of *M. rhesus* 17, in which animal the heart stopped beating during registration from the third electrocardiographic lead. In *M. rhesus* 12, on the morning of the fourth and last day of the disease, when the heart rate had become slowed from the normal of 205 beats per minute to 80 beats per minute, the rhythm became a little



Fig. 1.—Bradycardia of yellow fever. Upper tracing shows the heart rate and the duration of the P-R period in *M. rhesus* 12 before inoculation with the virus. Lower tracing represents the degree of bradycardia and the lengthened P-R interval in the same animal on the morning of the fourth day of the disease (Lead II).

irregular. So slight was this change that it could not have been detected except by graphic methods of registration; the variations in the intersystolic periods were never greater than 0.08 of a second. The difference in length between intersystolic periods in the rhythm of this heart ranged from 0.04 to 0.08 of a second. Table I which presents the variations in cardiac rate from day to day of the disease, as measured by electrocardiography, and Fig. 2 which presents the same data in graphic form, give a better conception of these changes than could be obtained from further description. Recourse may also be taken to the serial cardiographic tracings (Figs. 7 and 8) which depict among other occurrences the lengthening of the intersystolic period in some of these animals during the later course of the disease. The slowed heart rate, as compared with the normal, is also well shown in Fig. 1.

The effect upon the existing bradycardia of cutting the vagi is of peculiar interest. The results of the experiments in which this opera-

tion was performed demonstrate that the bradycardia occurring in rhesus monkeys during the course of their illness from yellow fever persists after bilateral section of the vagus nerves. In only one animal was vagus section followed by a heart rate more rapid than that existing before the operation; in this case a bradycardia of 80 beats per minute was replaced by one in which 104 cycles were recorded

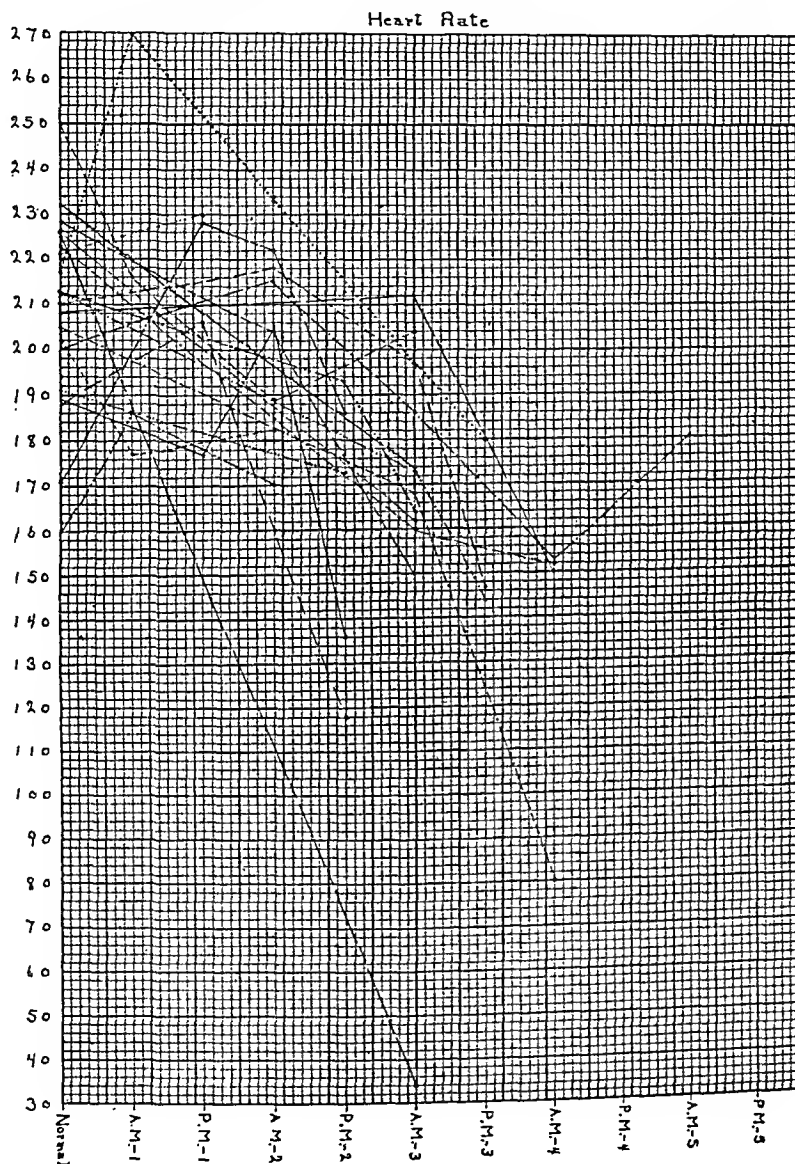


Fig. 2.—The heart rates of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae represent the time of the disease measured at twelve-hour intervals; the ordinates represent the rates of heartbeat. The curve for each animal is drawn in a different type of solid or broken line. The progressive nature in the development of the bradycardia is well shown in the downward trend of most lines toward the later days of the disease.

during the same period. It should be borne in mind, however, that the later recorded rate of 104 was still half the original cardiac frequency and represented a most marked bradycardia. In one instance in this series the heart rate remained the same before and after vagus sec-

tion, while in the other four instances it was even less following the operation than previously. The explanation of this latter effect is problematical, but may possibly be related to a slower filling of the heart chambers associated with the very much slower respiratory rhythm. A slight lengthening of the conduction time, as represented by the P-R interval of the electrocardiogram, was noted in five of the ten experiments. This increase in the P-R period was never greater than 0.02 of a second. Its occurrence recalls the effect of vagal section or of atropinization in increasing the A-V block which follows rapid auricular action.³⁸ With regard to this consideration it may also be noted that in the dog's auricle in many circumstances in which the transmission intervals are long, vagal stimulation shortens these and, where actual block exists, partially or wholly relieves the condition.^{37, 39, 36, 15, 16} In the remaining five experiments the conduction time was in one instance shortened, and in three instances unchanged, following the cutting of the vagi. The evidence of the control experi-

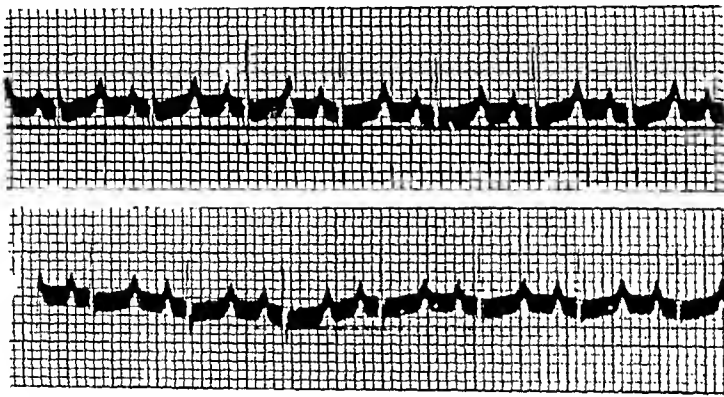


Fig. 3.—Independence of the bradycardia of yellow fever of vagus nerve influence. Upper tracing represents the heart rate in *M. rhesus* 2 before bilateral vagus section. Lower tracing shows the heart rate in the same animal following vagotomy.

ments suggests that even in normal monkeys the vagus nerve exerts little effect upon the heart rate during ether anesthesia. The latter suggestion is in keeping with the finding of Gold, Gryzwacz, and Nowicki²² that ether by inhalation, in doses that do not paralyze respiration, depresses but does not completely paralyze the vagi. In these control animals the heart rate was in two instances unaltered, on one occasion slightly raised, and upon another slightly lowered, following bilateral vagus section. Vagus influence upon the heart rate is known to be very fluctuating.⁴⁶ It is very well marked in the dog and to a lesser degree in man.⁴⁷ Vagus tone varies from species to species,⁵⁰ from animal to animal within the same species, and from time to time within the same animal. As Wenckebach and Winterberg⁶³ have pointed out, the bradycardia of sino-atrial origin is different from that responsible to vagus influence in that the former is a regular one, while the latter is irregular in its rhythm. It may be noted that the slow heart rate of yellow fever persists during anesthesia induced by

sodium iso-amyl-ethyl barbiturate given intraperitoneally in a dosage of 0.05 gram per kilogram of body weight. This result was consistent in the four animals of this series on which the drug was used. The amount given to one animal frequently equalled 100 to 150 milligrams, depending upon its weight. Lieb and Mulinos⁴² have shown that when 20 milligrams of sodium iso-amyl-ethyl barbiturate are

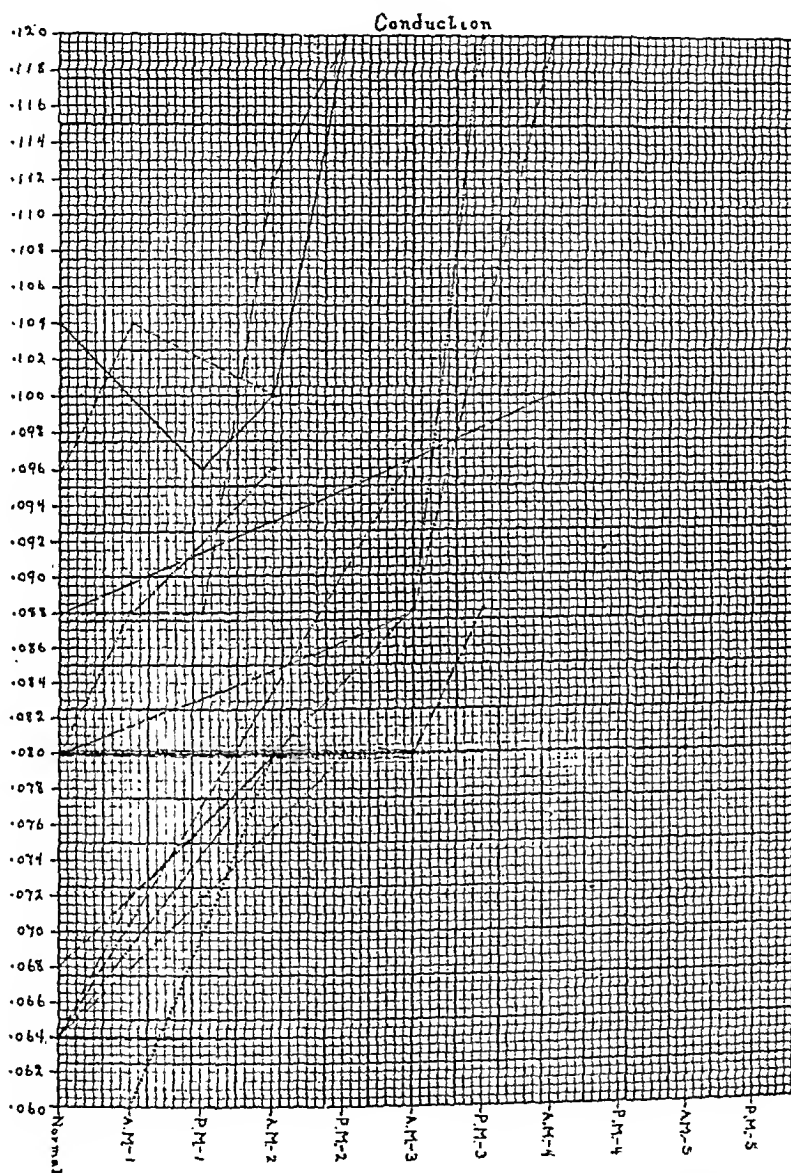


Fig. 4.—The conduction times, as measured by the P-R intervals of the electrocardiograms, of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae indicate the time of the disease process measured at twelve-hour intervals; the ordinates represent the time values of the P-R intervals measured in decimals (thousandths) of a second. The curve for each animal is drawn in a different type of solid or broken line. A progressive but not a constant trend toward lengthening of the conduction time during the progress of the disease is well shown.

given intravenously to a cat, prolonged, but temporary, paralysis of the vagus fibers to the heart results. These considerations are cited because it is believed that the evidence points to the concept that the

TABLE II
EFFECT VAGUS SECTION ON BRADYCARDIA OF MONKEYS EXPERIMENTALLY INFECTED
WITH YELLOW FEVER VIRUS

| MONKEY NUMBER | BEFORE VAGUS SECTION | | AFTER VAGUS SECTION | |
|------------------|----------------------|---------------------|---------------------|--------------------|
| | HEART RATE* | CONDUCTION† TIME | HEART RATE | CONDUCTION TIME |
| 6 | 180 | 0.08 | 156 | 0.088 |
| 2 | 150 | 0.10 | 150 | 0.104 |
| 16 | 174 | 0.08 | 158 | 0.10 |
| 7 | 180 | 0.08 | 172 | 0.08 |
| 9 | 135 | 0.08 0.096‡ | 120 | 0.08 |
| 12 | 80 | 0.12 | 104 | 0.14 |
| 21 C | 222 | 0.08 | 225 | 0.08 |
| 22 C | 246 | 0.056 | 234 | 0.06 |
| 23 C | 202 | 0.12 | 235 | 0.10 |
| 24 C | 252 | 0.08 | 252 | 0.08 |

*Heart rate recorded in beats per minute.

†Conduction time as indicated by P-R interval of the electrocardiogram, recorded in decimals of a second.

‡Traction on vagi.

C—Control experiment.

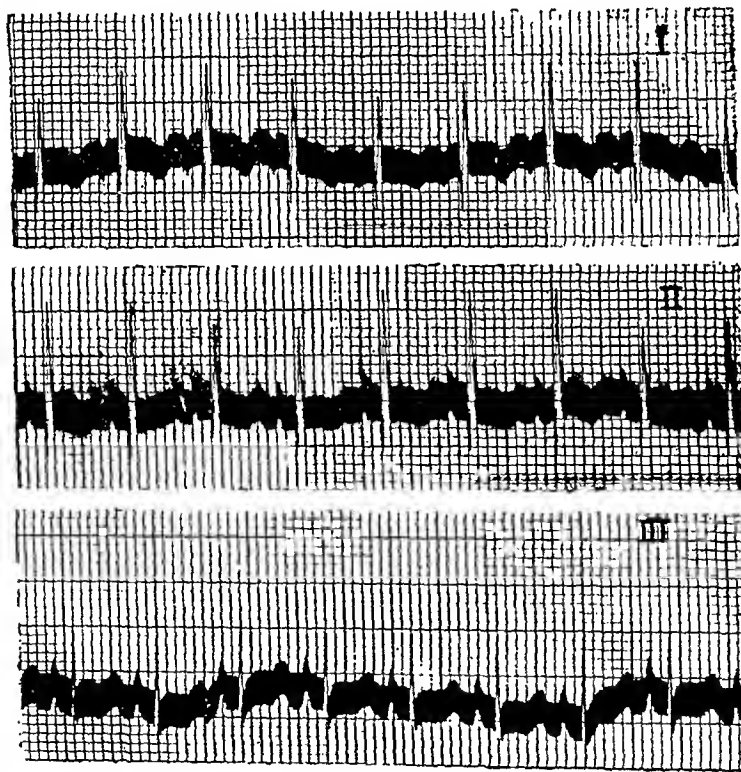


Fig. 5.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 12 on the morning of the third day of the disease. Note negative P_i and T_i deflections.

bradycardia of yellow fever is independent of vagus influence. Table II summarizes the results of the vagus section experiments; and in Fig. 3 electrocardiograms of the existing bradycardia in *M. rhesus* 2, before and after vagus section, are represented.

2. Physiological observations upon the auricular muscle.

Careful study of the character of the P-deflection during the course of the disease disclosed an infrequency of changes which could be

definitely recognized as abnormal. Nevertheless, in those infrequent instances when alterations in this wave were encountered, they were of the most profound kind. On two occasions in one animal (*M. rhesus* 4) the P-wave was reduplicated in Lead III during the first and second days of the disease. In another monkey (*M. rhesus* 6), it was found to be doubled in the tracing of Lead II, on the morning of the second day of the malady. In neither animal did these variations in the P-wave persist during the later progress of the infection. The reduplication of the P-deflection was in these instances inconstant from cycle to cycle, and frequently the second P-wave was observed to be negative in direction, thus imparting a diphasic character to the auricular tracing. Apart from these observations, purely negative P-waves occurred at one period of registration in the electrocardio-

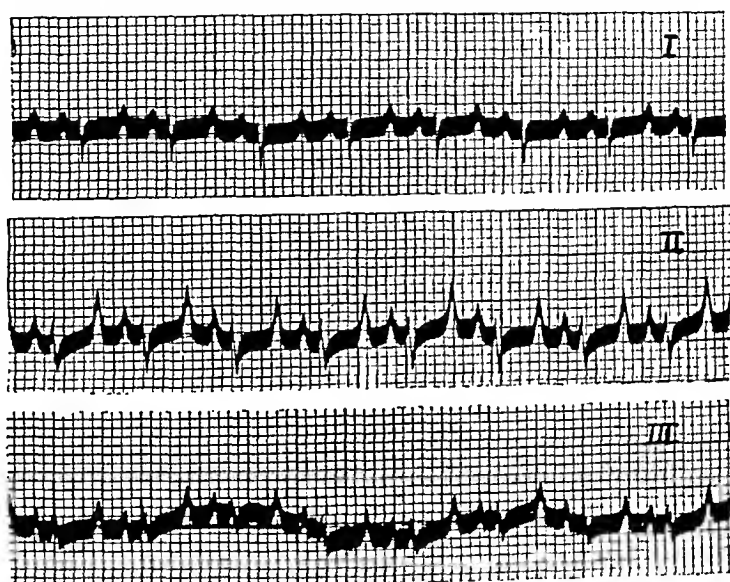


Fig. 6.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 19 on the morning of the third day of the disease. Note low voltage of R-wave and increased amplitude of S-wave in all leads: splintering of R_2 ; and markedly increased amplitude of T_2 and T_3 .

gram of Lead I, from another animal (*M. rhesus* 12) on the morning of the third day of the disease. This event is well shown in Figs. 5 and 8. In this instance the inverted wave was followed by a P-R interval 0.008 of a second shorter in duration than the normal for that animal. This change was not found in the tracing from the same lead of the same animal on the following day. The monkey was one which showed the most marked bradycardia in the series as well as marked alterations in the T-deflection.

3. Physiological observations upon the auriculo-ventricular bundle.

In these experiments the time required for the conduction of the excitation wave along the A-V bundle has been an important consideration. Observations upon the P-R interval of the electrocardiogram showed that in sixteen of the nineteen animals infected with yellow

TABLE III
CONDUCTION TIME OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS†

| MONKEY NUMBER | NORMAL | DAYS OF INCUBATION | | FIRST DAY FEVER | | SECOND DAY DISEASE | | THIRD DAY DISEASE | | FOURTH DAY DISEASE | | FIFTH DAY DISEASE | | RECOVERY PERIOD |
|------------------|--------|-----------------------|------|--------------------|--------|-----------------------|-------|----------------------|-------|-----------------------|------|----------------------|------|--------------------|
| | | 1 | 3 | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | A.M. | P.M. | |
| 1 | 0.104 | | | | 0.096 | 0.10 | 0.12 | D | | | | | | |
| 2 | 0.088 | | | | | 0.112 | 0.12 | D | | 0.10 | D | | | |
| 3 | 0.088 | | | 0.072 | 0.088 | 0.08 | | | D | | | | | |
| 4 | 0.064 | | | 0.104 | | 0.10 | | | | | | | | |
| 5 | 0.096 | | 0.10 | 0.06 | | 0.08 | D | | | | | | | |
| 6 | | | | | | 0.08 | | 0.08 | 0.08 | D | | | | |
| 7 | 0.08 | | | | | 0.096 | | 0.08 | | 0.08 | | | | |
| 8 | 0.08 | | 0.08 | 0.088 | | 0.08 | | 0.08 | | 0.08 | | 0.08 | D | |
| 9 | | 0.08 | | | | 0.08 | | | | | | | | |
| 10 | 0.08 | | | | | 0.08 | | 0.08 | D | | | | | 0.08 |
| 11 | 0.064 | | | | | 0.08 | | 0.08 | 0.088 | D | | | | |
| 12 | 0.088 | | | | | 0.096 | | 0.096 | | | | | | |
| 13 | 0.064 | | | | | 0.088 | | 0.088 | | 0.12 | D | | | 0.08 |
| 14 | 0.068 | | | | | D | | D | | | | | | |
| 15 | 0.064 | | | | 0.064* | | 0.08 | 0.088 | 0.12 | D | | | | |
| 16 | 0.08 | | | | | D | | | | | | | | |
| 17 | 0.08 | | | | | | | 0.08 | D | | | | | |
| 18 | 0.064 | | | | | 0.08 | | 0.32† | D | | | | | |
| 19 | | | | | | 0.08 | | 0.08 | D | | | | | |
| 20 | 0.064 | | 0.08 | | | 0.064 | 0.064 | D | | | | | | |
| Control | | | | | | | | | | | | | | |

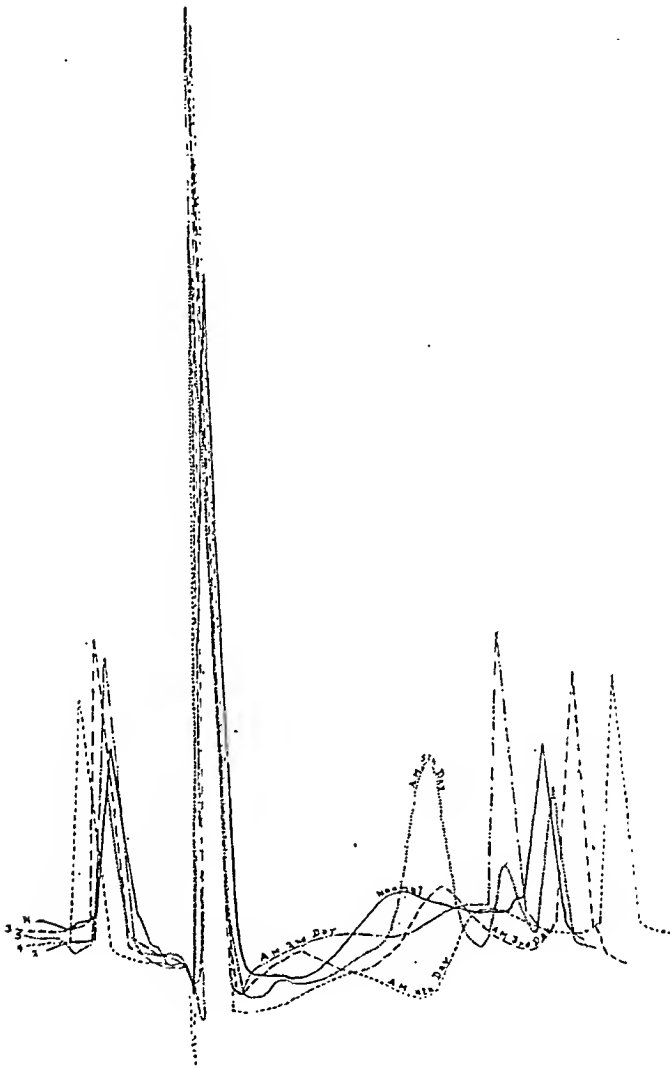
†Animal died during inscription of Lead III.

*Bled from heart, animal died.

†As indicated by P-R interval of electrocardiogram recorded in decimals of a second.

D—Animal dead.

fever virus, there occurred prolongation of the conduction time, usually slight in degree. Moreover, with few exceptions the delay in conduction was progressive, increasing from day to day of the disease. In one of the two animals which recovered, the conduction period had



Macacus rhesus 7
Lead III

Figs. 7 and 8.—In each figure, outline drawings of a specific electrocardiographic lead from one animal are reproduced. The series of tracings composing a figure represents normal electrocardiograms and electrocardiograms taken at varying intervals during the course of the disease. The method of their preparation consisted in the projection upon a screen of lantern slide reproductions of the various electrocardiograms from a given animal. Employing always the same magnification, a representative cardiac cycle was selected in each lantern slide, and its outline was traced upon white paper. Succeeding cycles were so projected that the points of onset either of the Q- or R-waves of serial cycles were made to coincide. From this fixed point in each series the outlines were always traced. The time of annotation of each electrocardiogram is noted upon the figures. This method of illustration shows well the variations in the length of the entire cardiac cycle from day to day of the disease, the variations in the duration of the P-R and R-T periods, and especially well the deformities of the R-T period and the T-wave during the course of the disease.

lessened during convalescence but at the last period of observation had not yet regained its normal time interval. It should, however, be noted that in this instance the last record was taken only four days

following the first appearance of fever. In the other recovered monkey the conduction time had returned to normal by the last day of observation. In this case the final registration was secured twenty-five days after the animal had first shown fever.

On one occasion the A-V conduction time was approximately doubled during the course of the disease. In three instances it was increased by approximately half its normal value. Just before death in one animal the P-R interval measured 0.32 of a second as contrasted with the normal period in the same animal of 0.08 of a second. Excluding from the series this one extreme value, the average greatest increase in the conduction period equalled 0.014 of a second. The

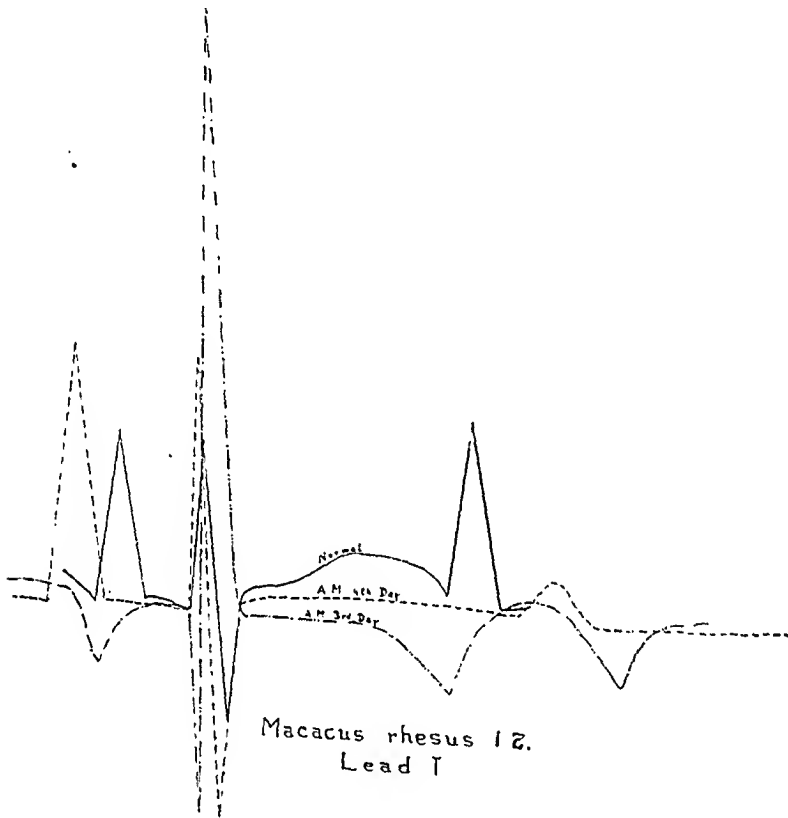


Fig. 8.

average normal value was 0.078 of a second, while the average longest period in each animal during the course of the disease was 0.092 of a second. The fact is significant that no increase in the P-R interval of the electrocardiogram occurred in the control animal dying from a peritoneal infection after a period equal in duration to the average course of yellow fever in the monkey. Table III epitomizes the detailed information regarding these variations. In Fig. 4 the P-R periods for the various animals have been plotted in graphic form, so that it may be possible to visualize the degree of the delay in conduction. The lengthening of the P-R interval on successive days of the disease is well shown in the serial cardiographic tracings (Figs. 7 and 8).

In these experiments the occurrence of altered and reduced con-

duction in the auriculo-ventricular bundle branches has been suggested in the occasional observance of definite widening of the base of the R-wave and, in one instance, of distinct notching of the apex of this deflection in a tracing taken from Lead III on the morning of the third day of the disease. That in this instance the evidence of a broadened base of R with notching of its apex is significant, is further rendered likely by the occurrence of a concurrent reversal of preponderance. At the same time T became of greatly increased height in a positive direction in all leads, while S assumed a considerably increased amplitude in Leads I and II, where it formed the most prominent "spikes" of the tracings. The several findings in the electrocardiograms from this animal are in keeping with the occurrence of a partial branch-bundle block.

Direct comparison of the conduction time with the heart rate shows in general a correspondence between the two phenomena. It has been observed that the cardiac rate of contraction decreases, while the conduction time increases during successive days of the disease. It must be noted, however, that the correspondence is an approximate and not an absolute one.

4. *Physiological observations upon the ventricular muscle.*

The study of the ventricular portion of the electrocardiogram divides itself naturally into the consideration of three groups, the QRS complex, the R-T period, and the T-wave itself.

The QRS Period.—In a review of observed alterations in the QRS portions of the ventricular electrocardiogram, the consideration of the amplitude of the different waves, except in especial instances, will be purposely avoided, because it is not believed to be a significant point. In these experiments there were very evident variations in the amplitude of the deflections from one tracing to another of the same heart at different times, both in health and during the course of the disease. The voltage of a tracing, taken on the last day of the disease, might be either higher or lower than that of the normal electrocardiogram of the same animal. That changes of amplitude of qualitative significance may occur, however, is supported by the appearance of certain alterations of unusual incidence associated with other and more significant changes. An S-wave, previously absent or poorly defined in Lead III, has during the course of the disease been observed to become of considerable amplitude, and in association with a diminution in the size of R, to assume the place of the most prominent "spike" in the tracings. Similarly S, a badly demarcated wave in Leads II and III of the electrocardiograms taken before inoculation of the animal with yellow fever virus, has been seen to become of marked amplitude with a diminution of the R-wave in the same leads on the later days of the disease (Fig. 6). Not infrequently a Q-wave barely discernible in Lead I of the normal tracing had attained so great an amplitude, in

later stages of the disease, as to appear as the most prominent "spike" in the electrocardiogram from the same lead. Changes in preponderance from day to day of the disease have been commonly noted. A splintering of the R-wave in Lead III has been found associated with variation in the amplitude of the associated deflections of the ventricular electrocardiogram (Fig. 6).

The R-T Period.—A much more definite change observed in the ventricular electrocardiogram during experimental yellow fever resembles changes of similar form described by Pardee⁴⁹ as evidence of blocking of a branch of the coronary artery, and by Cohn and Swift⁵¹ as well as Rothschild, Sacks, and Libman,⁵⁴ as occurring in the acute phases of rheumatic fever. This change consists in deformity of the R-T or S-T period of the electrocardiogram. A significant deviation of this portion of the electrocardiogram is that which occurs when the downstroke of the R-wave fails to reach the base line, but instead commences abruptly upon a curve, convex upwards, occupying the entire R-T period, and becoming finally incorporated in the upstroke of the T-wave, so that it appears that the latter is given off directly from the R-wave. In other instances and even in the same tracing, the descending limb of the R-wave may extend below the line of equipotential to form a rounded S-wave, when the R-T segment, instead of occupying an almost horizontal position, may slope upward or downward to form an acute angle with the horizontal base line, and to merge itself gradually without appreciable distinction into the T deflection, thus imparting to the latter a diphasic appearance. While these two types of deformity of the R-T segment of the electrocardiogram represent changes typical of the later stages of experimental yellow fever, no specificity is attached to them, nor is it implied that these changes are of most frequent occurrence. They represent rather the more definite types of alteration among a series of changes comparable to them, which differ from them only unimportantly in their contours, and which exist with them in the same electrocardiographic series and even in the same tracing. The serial electrocardiographic tracings (Figs. 7 and 8) show clearly this pleomorphism in the contour of the R-T period in the electrocardiograms of yellow fever.

Observations upon the length of the R-T interval showed that in eighteen of the nineteen animals studied electrocardiographically during the course of infection with experimental yellow fever, an increase was noted in the duration of this period. The prolongation of the R-T interval was progressive in character and increased from day to day of the disease. There was in general a parallelism in the progressive increase in length of the R-T period with that of the R-R period, but the relation was by no means a constant one. While the ratios between the durations of the two periods showed in many instances an approximate correspondence, in others they presented wide divergence. In three experiments, lengthening of the period became so

marked that T encroached on the following P-wave or else the latter became superimposed on the T deflection. The control animal suffering from an infection of the peritoneum also presented a lengthening of the R-T period. The only animal in this series which did not show lengthening of the R-T interval recovered from the disease. The other recovered animal presented prolongation of this period during the course of the disease, with subsequent shortening during convalescence. In the light of our present knowledge of electrocardiography, it is impossible to determine the significance of the lengthened R-T period. The lengthening of the period is also shown in Figs. 7 and 8.

The T-wave.—The results of the study of the T-wave of the electrocardiogram in experimental yellow fever reveal certain observations which are significant because of their frequency and uniformity of occurrence. These changes warrant consideration. It has been noted that in fourteen of the nineteen animals infected with yellow fever virus, the character of the T-wave became altered in the end stages of the disease, becoming in one or more leads either diphasic, reduplicated, negative, or accentuated in its inscription. These deformities of the T-wave were independent of alterations in the initial ventricular deflections (QRS complexes). The normal upright terminal wave of the ventricular electrocardiogram was incessantly replaced by a deflection either negative in direction, or diphasic in contour, the latter presenting either two waves above the line of equipotential or one positive and one negative wave in relation to the base line (Figs. 5, 7, 8). Exclusive of these types of deformity of the terminal deflection, an upright T-wave of increased height associated with other electrocardiographic changes has been a common finding (Fig. 6). An accentuated terminal deflection has, however, been observed upon two occasions in tracings from normal animals.

Two of the five animals (*M. rhesus* 8 and *M. cynomolgus* 11) which failed to show alterations in the T deflection recovered from the disease. The remaining three animals were not fairly representative of the course of the experiment, as each died prematurely of early or only moderately advanced yellow fever lesions, hastened in their death in two instances (*M. rhesus* 1 and 3) by the coma and subnormal temperature induced by the administration of sodium iso-amyl-ethyl-barbiturate, and in a third (*M. rhesus* 15) by the loss of blood following a cardiac bleeding. Nevertheless, even with these animals included in the series, the incidence of aberrant T deflections is a noteworthy one, occurring as it did in 74 per cent of the monkeys dying of yellow fever. A study of the time relationship of these changes to the course of yellow fever reveals the fact that the abnormal variations appeared most frequently on the latter days of the disease. In nine of the thirteen animals in which they were observed, these alterations were first noted on the day of death. In five of these nine cases it had been

possible to obtain tracings on the monkeys on the day previous to death; the electrocardiograms taken on this day showed normal T deflections. In two animals the abnormal waves were first inscribed on the day preceding death and in one they were first noted two days previous to the animal's death. In seven of the fourteen instances in which significant alterations in the T-waves existed, negative deflections were observed in either Lead I or Lead II, or in both of these leads (Fig. 5). This fact is pointed out not because it is believed that the negative variations were the most significant of those noted, but rather because in a purely empirical way we know most about this type of change in the T-wave. Before leaving the consideration of the terminal portion of the ventricular electrocardiogram in yellow fever, it is important to note the ephemeral character of any given deformity either of the R-T period or of the T-wave. These disturbances are transient, fleeting in nature, present in one tracing and not in another, one type of variation being inscribed upon one occasion, and a different deformity appearing during subsequent inscriptions. The variations of the T deflections and of the R-T period during the course of the disease are well represented in the serial electrocardiographic tracings (Figs. 7 and 8).

DISCUSSION

A perusal of the literature upon bradycardias of sino-atrial origin engenders the belief that those types of sino-auricular block which are invariably associated with irregular or inconstant forms of bradycardia, and which occur in relatively normal hearts, possess nothing in common with the retarded heart rate of yellow fever. That a relationship may exist between some types of the so-called sino-auricular block and the bradycardia of yellow fever, is, however, rendered problematical in view of the observations of MacKenzie⁴⁵ and Riebold.⁵⁰ The former author first described the condition as occurring in influenzal myocardial involvement, and suggested "that the heart symptoms in this case, and it may be in the slow irregular hearts in diphtherial cases, are due, not to vagus stimulation but to a poison acting like digitalis, directly on the heart itself." Riebold also expressed the belief of a relation of sino-auricular block to infectious diseases. More recently Cohn and Swift¹¹ have reported the occurrence of sino-atrial block in the course of rheumatic fever; and Smith⁶⁰ has recorded its incidence in diphtheria. A type of sinus bradycardia closely resembling that of experimental yellow fever, has been reported by Winternitz and Selye⁶⁸ as a result of thrombosis of the artery to the sino-atrial node.

In the consideration of the relation of jaundice to the slow cardiac rhythm of yellow fever, certain observations are of value. The fact is so well known that bradycardia is frequently a concomitant manifestation of the icteric state that a second fact needs to be empha-

sized, namely, that the association is by no means a universal one.^{51, 67, 6} Every experienced observer has seen numerous cases in which the most marked degrees of jaundice were accompanied by a rapid pulse. The facts that a retarded cardiac rate is a constant phenomenon in experimental yellow fever, and that jaundice is very inconstantly associated with slow heart action, offer an inconsistency which militates against the possibility of a causal relationship of the ieterus to the bradycardia in this disease. The bradycardia associated with ieterus is of an irregular type,⁶⁷ whereas that of yellow fever is a regular one. Moreover, in yellow fever bradycardia may occur independently of jaundice, and in the presence of a normal bilirubin content of the serum.⁴

The hypothesis which Chagas has advanced that the bradycardia of yellow fever is a part of a "suprarenal syndrome" fails to attain credence in consideration of the fact that in the two cases in his series in which suprarenal lesions were found at autopsy the degeneration was confined to the cortical zones.⁶¹

In the auricular electrocardiograms of yellow fever, the occurrences of reduplicated and more especially of inverted P-waves, though infrequent, are of importance. A negative P-wave has been regarded by many workers^{31, 32, 52, 47, 25, 65, 66, 7, 23, 13} as indicating a shifting of the pacemaker from its normal position in the upper extremity⁴⁰ of the S-A node to a lower functional level in the sinus node, auricle or A-V node. Negative P-waves can be produced experimentally in the tracings taken from animals during vagus stimulation, in which instance they may be abolished by atropine.^{27, 17, 24, 26, 18} In some cases, however, negative P-waves persist after atropinization, and do not change on compression of the vagus nerve in the neck.⁷ Wiggers⁶⁴ believes that in these instances, the sino-atrial node should not be thought to be the seat of disease, unless the inverted waves are associated with a reduced or a reversed P-R interval, or are accompanied by auricular extrasystoles or periodically give rise to tachycardia.

The lengthening of the P-R interval of the electrocardiogram, moderate in degree, which has been observed with considerable constancy during the course of experimental yellow fever, is indicative of an impairment of function in the auriculo-ventricular bundle.

In experimental yellow fever the changes in the ventricular electrocardiogram are of especial interest. Because of the considerable amount of evidence which has been obtained in recent years relating to alterations in the T-wave of the electrocardiogram, which have been observed during the course of many disease conditions provocative of damage to heart muscle, it is important that we should consider the changes in the terminal deflections which have been so frequently encountered during the course of experimental yellow fever. The observations on the latter disease are of singular significance in that in this instance the opportunity has been afforded of correlating these func-

tional aberrations with the findings of histopathology in the precise muscular tissue in which they were produced only a few hours antecedent to the fixation of the tissue. This privilege obtains only in a few diseases, and in still fewer may the study be conducted under the more readily controlled methods of animal experimentation. Observations relating to the histopathological changes in the myocardial tissues in this series of animals will be published in another paper.

General acceptance is accorded the view that the initial portion of the ventricular electrocardiogram, the QRS complex, represents a composite tracing of the differences in electrical potential set up in the plane of the lead by the wave of excitation passing throughout both ventricles.^{41, 33, 34} The period between R and T or between S and T, which in the normal electrocardiogram usually follows the base line, indicates an electrical equilibrium in the cardiac musculature in the plane of the lead at that time, and implies that a state of excitation exists throughout the ventricles. The frequent divergence of this portion of the curve in yellow fever suggests a disturbance of those stresses which normally during this period repose in equilibrium.

In view of our present information upon this subject, no justification exists for attaching a specific significance to a single form of alteration in the contour of the end deflection. The occurrence of one type of deformity of the T-wave at the time of registration of a given lead, and of another deformity in the same lead at another time of recording during the progress of the disease, suggests a common basis for these aberrations and an existing relationship between them. Rosnowski³³ has noted the occurrence of changes in the end deflection in the course of intoxications which, like yellow fever, result in diastolic arrest of the ventricles. The common observance of the markedly accentuated T-wave with a high, sharply vertical summit during the later days of the disease may, with caution, be tentatively accepted as a deformity of the terminal deflection of undetermined significance. There is no evidence of a different pathological interpretation of a T-curve which is diphasic in contour from one solely negative in direction. The incidence of abnormal deflections in more than one lead from the same animal, and their occurrence in the first and second leads, would seem to be more important than a solitary incidence of the change, especially if the latter presented itself in Lead III alone. In the extent of existing knowledge it is only justifiable to attribute to these T deflections of proved altered and abnormal contour, whether they be inverted, diphasic, or doubly positive in direction, the general significance of an abnormal retreat of the excitation process. They are signs that the myocardium is not behaving normally.

The consideration which the presented observations make desirable of emphasis is that well-marked deformities of the T-wave, such as are never observed in the healthy animal under the conditions of the experiment, are recorded with considerable constancy of occurrence

on the latter days of the disease, at a time at which subsequent observations have shown that advancing myocardial degeneration is taking place in the ventricles. For these reasons the suggestion is advanced that alteration in the end deflection of the electrocardiogram may afford valuable information of functional injury to the ventricular muscle. This concept is further supported by the fact that alterations in the T deflection were absent in the two animals in the series studied which recovered from the disease, while they were present in all the monkeys which died, with uncomplicated lesions of yellow fever, at the end of a complete course of the infection. The deformities of the T-wave were also not observed in the animal dying from peritonitis at the end of a comparable period.

SUMMARY

1. Bradycardia, regular in rhythm, absolute in degree, and progressively more marked on succeeding days of the disease, has been a constant finding in experimental yellow fever in the monkey; the phenomenon persisted independently of ether anesthesia, sodium iso-amyl-ethyl barbiturate anesthesia, and bilateral section of the vagus nerves.

2. Reduplication of the P-wave of the electrocardiogram was occasionally observed in experimental yellow fever; more rarely this deflection was seen to be inverted.

3. Prolongation of the conduction time of the auriculo-ventricular bundle was observed in slight or moderate degree in 84 per cent of cases.

4. Among electrocardiographic alterations referable to the ventricular muscle during the course of the disease, changes in ventricular preponderance were commonly observed. The R-T period was lengthened in 94 per cent of cases; and frequently it was deformed. The normal upright T-wave was replaced in 74 per cent of cases by a deflection either negative in direction, diphasic in contour, or increased in height.

The author wishes to express his appreciation of much valuable advice afforded him by Professor Oskar Klotz during the course of the study. He is also indebted to Dr. A. E. Cohn and to Dr. J. Hepburn for many helpful suggestions.

REFERENCES

1. Aitken, Connal, Gray, and Smith: *Tr. Roy. Soc. Trop. Med. & Hyg.* 20: 166, 1926.
2. Aitken and Smith: *Tr. Roy. Soc. Trop. Med. & Hyg.* 20: 530, 1927.
3. Aitken and Smith: *Conférence Africaine de la Fièvre Jaune. Dakar. Avril, 1928*, pp. 60, 67, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
4. Berry and Kitchen: Personal communication.
5. Boyce: *Yellow Fever and Its Prevention*, London, 1911, John Murray.
6. Cannell: *Am. J. Path.* 4: 431, 1928.
7. Carter and Wedd: *Arch. Int. Med.* 23: 1, 1919.
8. Chagas: *Compt. rend. Soc. de biol.* 99: 1664, 1928.
9. Chagas and de Freitas: *Mem. do Inst. Oswaldo Cruz* 7: 72, 1929.
10. Cohn and Noguchi: *J. Exper. Med.* 33: 683, 1921.
11. Cohn and Swift: *J. Exper. Med.* 39: 1, 1924.

12. Coll y Toste: *An. méd. Puerto Rico*, San Juan 1: 43, 1912.
13. Cowan and Fleming: *Lancet* 213: 1064, 1927.
14. Delmas: Quoted by Tonatre, *New Orleans M. & S. J.*, 1898.
15. Drury and Andrus: *Heart* 11: 389, 1924.
16. Drury and Andrus: *J. Physiol.* 59: 41, 1924-25.
17. Einthoven: *Arch. f. d. ges. Physiol.* 122: 517, 1908.
18. Einthoven, Fahr, and De Waart: *Arch. f. d. ges. Physiol.* 150: 275, 1913.
19. Elliott: *Arch. Int. Med.* 25: 174, 1920.
20. Paget: *Monographie sur le type et la spécificité de la fièvre jaune établis avec l'aide de la montre et du thermomètre*, Paris, 1875, J. B. Bailliére et Fils.
21. Fowler, Simpson, Ross, and Leishman: *Second Report of the Yellow Fever Commission (West Africa)*, London, 1914, Waterlow and Sons.
22. Gold, Gryzwacz, and Nowicki: *AM. HEART J.* 4: 336, 1929.
23. Hamburger: *Arch. Int. Med.* 26: 232, 1920.
24. Hering: *Arch. f. d. ges. Physiol.* 127: 155, 1909.
25. Hering: *München. med. Wchnschr.* 61: 2057, 1914.
26. Von Hoesslin: *Deutsche Arch. f. klin. Med.* 113: 537, 1914.
27. Kahn: *Arch. f. d. ges. Physiol.* 140: 627, 1911.
28. Klotz: Personal communication.
29. Lasnet: *Conférence Africaine de la Fièvre Jaune*. Dakar. Avril, 1928, page 32, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
30. Lebrede: *Yellow Fever Bur. Bull.* 1: 294, 1911.
31. Lewis: *Brit. M. J.* 1: 750, 1910.
32. Lewis: *Heart* 2: 23, 1910-11.
33. Lewis: *Phil. Tr. Roy. Soc., London*, series "B," 207: 221, 1916.
34. Lewis: *Arch. Int. Med.* 30: 269, 1922.
35. Lewis: *The Mechanism and Graphic Registration of the Heart Beat*, London, 1925, ed. 3, page 131, Shaw and Sons.
36. Lewis and Drury: *Heart* 10: 179, 1923.
37. Lewis, Drury, and Bulger: *Heart* 8: 83, 1921-22.
38. Lewis, Drury, and Ilescu: *Heart* 9: 21, 1921-22.
39. Lewis, Drury, Ilescu, and Wedd: *Heart* 9: 55, 1921-22.
40. Lewis, Oppenheimer, and Oppenheimer: *Heart* 2: 147, 1910-11.
41. Lewis and Rothschild: *Phil. Tr. Roy. Soc., London*, series "B," 206: 181, 1914-15.
42. Lieb and Mulinos: *Proc. Soc. Exper. Biol. & Med.* 26: 709, 1929.
43. Lins: *a Folha med.* 9: 218, 1928.
44. Macfie and Johnston: *Yellow Fever Bur. Bull.* 3: 121, 1913-1915.
45. Mackenzie: *Brit. M. J.* 2: 1411, 1902.
46. Macleod: *Physiology and Biochemistry in Modern Medicine*, ed. 5, p. 440, St. Louis, 1926, The C. V. Mosby Co.
47. Meek and Eyster: *Heart* 5: 227, 1913-14.
48. Noguchi: *J. Exper. Med.* 29: 547, 1919.
49. Pardee: *Arch. Int. Med.* 26: 244, 1920.
50. Riebold: *Ztschr. f. klin. Med.* 73: 1, 1911.
51. Riegel: *Ztschr. f. klin. Med.* 17: 221, 1890.
52. Ritchie: *Quart. J. Med.* 6: 47, 1912-13.
53. Rosnowski: *Compt. rend. Soc. de Biol.* 100: 211, 1929.
54. Rothschild, Sacks, and Libman: *AM. HEART J.* 2: 356, 1927.
55. Sawyer, Lloyd, and Kitchen: *J. Exper. Med.* 50: 1, 1929.
56. Seidelin: *Berl. klin. Wchnschr.* 46: 821, 1909.
57. Seidelin: *Yellow Fever Bur. Bull.* 1: 134, 1911.
58. Selwyn-Clarke: *Conférence Africaine de la Fièvre Jaune*. Dakar. Avril, 1928, p. 138, Imprimerie Militaire Universelle L. Fournier, Paris, 1929.
59. Smirnow and Olefrenko: *Ztschr. f. d. ges. exper. Med.* 57: 559, 1927.
60. Smith: *J. A. M. A.* 77: 765, 1921.
61. Torres and Azevedo: *Compt. rend. Soc. de Biol.* 99: 1673, 1928.
62. Tonatre: *Yellow Fever—Clinical notes*, translated from the French by Charles Chassaiguac, *New Orleans M. & S. J.*, 1898.
63. Wenckebach and Winterberg: *Die unregelmässige Herztätigkeit*, Textband, Leipzig, 1927, p. 132, Wilhelm Engelmann.
64. Wiggers: *Modern Aspects of the Circulation in Health and Disease*, ed. 2, p. 285, Philadelphia and New York, 1923, Lea & Febiger.
65. Wilson: *Arch. Int. Med.* 16: 86, 1915.
66. Wilson and Robinson: *Arch. Int. Med.* 21: 166, 1918.
67. Windle: *Brit. M. J.* 1: 123, 1916.
68. Winternitz and Selye: *Wien. Arch. f. inn. Med.* 16: 377, 1929.

THE MYOCARDIUM IN YELLOW FEVER

II. THE MYOCARDIAL LESIONS IN EXPERIMENTAL YELLOW FEVER*

WRAY LLOYD
TORONTO, ONT.

INTRODUCTION

IN A PRECEDING paper in this Journal the myocardial function registered by electrocardiography in rhesus monkeys during the course of experimental yellow fever, has been described. In this communication it is desired to present the evidence of histopathological alterations in the myocardial tissues of the group of animals upon which electrocardiographic tracings were obtained, supplemented by the results of the study of tissues from other animals in which the heart-beat had not been recorded during the course of the disease. Finally, it is hoped in some degree to correlate the graphic records of the disturbances of the heart action with the findings on microscopic examination of the tissues in which the disturbances arose.

The examination of numerous reports and descriptions of the gross and microscopic pathological conditions of the heart muscle in yellow fever reveals a remarkable discrepancy of observation and opinion. The conflicting evidence can be explained in part by the fact that all observers were not studying yellow fever. In addition to this consideration, the intensity of the lesions has undoubtedly varied in different epidemics and in individual cases.

Sodre and Couto,¹⁷ in 1901, observed the occurrence of hemorrhagic foci in the heart muscle, pericardium, and endocardium, noting as well the flabby condition of the myocardium in yellow fever. The aortitis and endocarditis which these authors described must be regarded as evidence of either antecedent or secondary infection. Microscopically, they found a patchy, fatty degeneration of the muscle fibers, occasional loss of cross striation in the sarcoplasm, and irregularity of size, form, and staining reactions of the nuclei.

In 1905 Otto and Neumann,¹⁴ and later Otto,¹³ described the heart muscle in yellow fever as showing all stages macroscopically from cloudy swelling to fatty degeneration. Microscopically, they observed a well-marked though delicate, irregularly distributed, fatty degeneration of the fibers; but these changes were less marked than those which they expected to observe from the consideration of the macroscopic appearances of the muscle.

The following year Marchoux and Simond¹² in their study of the dis-

*These studies have been performed under the tenure of a grant from the Banting Research Foundation. All the specimens used in the study were kindly made available by the International Health Division of the Rockefeller Foundation.

From the Department of Pathology and Bacteriology of the University of Toronto.

case noted only a slightly marked fatty degeneration of heart muscle, which though it affected some fibers, left others, in their opinion, in a nearly healthy state.

In 1912 Rocha Lima¹⁵ described the myocardium in yellow fever as soft and clay-colored, presenting microscopically the occurrence of more or less extensive, irregularly distributed granular and vacuolar degenerations. The nuclei of the muscle fibers were always well stained but often of conspicuously large dimensions. The muscle fibrillae and cross striations were constantly clearly discernible.

During this period Seidelin,¹⁶ writing of the pathology of yellow fever, reported the condition of the heart muscle in the disease as macroscopically pale or irregularly streaked or spotted in color, and diminished or friable in consistency. Histologically a fatty metamorphosis of the fibers could be observed.

Elliott,⁶ in 1920, noted loss of nuclei and cross striations in the most severely damaged muscle fibers. Six years later Aitken and his co-workers¹ recorded the occurrence of vacuolization in the myocardial fibers.

In 1927 Klotz¹⁰ described the changes in the heart muscle in yellow fever as degenerative ones unaccompanied by inflammation and affecting the myocardium in all its parts, including the auriculo-ventricular conducting system. Dilatation of the left ventricle was not uncommonly observed, and the muscular walls were soft and flabby as a result of granular and fatty degenerative changes in their substance.

A year later Cannell² recorded accurately in *Homo sapiens* and *Macacus rhesus* the patchy and irregular distributions of the fatty and granular degenerations, noting that in each fiber the former change was most marked about the nucleus. The pathological findings were essentially similar in the two species. Degenerative changes were present in both the ordinary myocardial muscle and the auriculo-ventricular bundle.

Contemporary with Cannell's observations, Hudson⁹ reported the occurrence of an irregularly distributed fatty degeneration of the cardiac fibers in monkeys experimentally infected with yellow fever, but found little change of cellular structure in the study of ordinary paraffin sections. The occurrence of congestion and less often of hemorrhage in the myocardial capillary bed was noted by the latter author.

In 1929 Fialho,⁷ describing the pathological findings in the recent epidemic of yellow fever in Brazil, noted pericardial and endocardial hemorrhages, dilatation of the right ventricular cavity, and fatty degeneration of the muscle. He believed the fatty change to have been more marked on the right side of the heart.

TECHNICAL METHODS

Selection of Material.—The material utilized for histopathological study consisted of the myocardial tissues of nineteen animals studied electrocardiographically

during infection with yellow fever virus, and of blocks of heart muscle from fourteen other monkeys, in which the myoeardial function had not been examined during the course of the disease. A study of sections of liver, kidney, and spleen in these animals verified the existence of yellow fever. As a control to the investigation of the cardiac histopathology, comparable tissues were examined from four animals studied electrocardiographically as controls in vagotomy experiments, as well as blocks from various regions of heart muscle from five other healthy rhesus monkeys. As an adjunct to this study and for purposes of comparison, the myoeardial tissues were examined from cases of acute yellow atrophy of the liver, eclampsia, and diphtheria in man.

Selection of Blocks.—All the blocks of heart muscle taken from the animals examined electrocardiographically were fixed in Zenker's fluid. Of the remaining yellow fever and control animals, some tissues were fixed in Zenker's fluid while others, in order to offer a greater breadth of study, were fixed in a 10 per cent formalin solution. Blocks of tissue were excised from these hearts in four representative regions, the sulcus terminalis region of the superior caval-auricular junction, the upper ventricular and lower auricular septal region, including the membranous portion and septal curtains of the tricuspid and aortic valves, and longitudinal areas of the musculature of the right and left ventricles. In special instances, in both diseased and healthy hearts, large blocks of the septum were cut out to include the coronary sinus region posteriorly and the anterior border of the membranous septum anteriorly. Serial sections taken through such blocks offered an opportunity for study of the auriculo-ventricular node and the crux commune of the auriculo-ventricular bundle at various levels of its course.

From blocks of tissue including the superior caval-auricular junction serial sections were cut from above downward in a plane at right angles to the course of the superior vena cava through the region of junction of that vessel with the musculature of the right auricular appendix. The sino-atrial node was invariably demonstrable in these sections situated deeply to the sulcus terminalis, as a well-defined, crescent-shaped group of fibers situated subendocardially, coursing around the caval mouth for a distance of 2.5 mm. on its right anterolateral aspect. Serial sections, taken through the greater part of the depth of the node, were prepared from twenty-seven monkey hearts. In this group there were five control series, eighteen series of paraffin sections from yellow fever hearts showing slow cardiac rate of beating during life, one series from an animal studied electrocardiographically during infection of the peritoneum, one series from an animal dying prematurely due to operative cardiac bleeding, and three series of frozen sections from yellow fever animals not studied electrocardiographically.

The auricular muscle was examined in microscopie preparations from twenty-nine monkey hearts. In this group there were twenty-seven series of paraffin sections and two series of frozen sections. Six control and twenty-three yellow fever animals are represented in the group.

The condition of the auriculo-ventricular bundle was investigated by the method of serial section in five yellow fever and three control animals. Sections of diseased and control tissues were compared from level to level through the course of the bundle. This method of study is of considerable importance in any investigation of the histopathology of the auriculo-ventricular bundle, because of changing cytological characters in the component cells, as the fibers of the crux commune course from the region of the auriculo-ventricular node to the forking of the bundle stem. Vacuolization and a loosely granular cortex are histological findings which ought to be regarded as normal in the latter region, whereas their occurrence in the former should excite the suspicion of degenerative change. With these considerations in mind, sections of control and diseased tissue from approximately the same levels have been compared in this study.

Blocks for section were taken from the ventricular musculature, both right and left, of forty hearts. In this series the tissue was obtained from thirty-six monkeys dying of yellow fever and from four healthy animals of the same species.

Methods of Staining.—Paraffin sections of the sino-atrial node, auricular muscle, auriculo-ventricular bundle, and ventricular muscle were stained by various methods, of which the hematoxylin and eosin and phloxin-azure B. methylene blue technics were most frequently employed. Less often special sections were stained by iron hematoxylin and eosin, the Giemsa stain, or Mallory's orange-G methylene blue connective tissue stain. Frozen sections cut from each of these regions were stained for fifteen hours in Sudan III.



Fig.1.—Sino-atrial nodal musculature in yellow fever. The darker areas along the course of the fibers represent areas of hyaline change. In intervening areas the protoplasm appears rarefied. In several fibers karyolysis has resulted in loss of nuclei. (Hematoxylin and eosin.)

RESULTS

1. *Histological observations on the sino-atrial node.*

The microscopic preparations of the sino-atrial node from animals dying of yellow fever presented histopathological changes both in the sino-atrial muscle and in the ganglion cells in proximate or immediate relation with the muscle fibers. In paraffin sections two different types of alteration were noted in these fibers. A patchy, hyaline-like change of the specialized muscle fibers, irregular in distribution and present as a splash-like accentuation of the acidophilic dye in any field, was the characteristic of the first type of lesion (Figs. 1 and 2). Areas of cytoplasm in these cell groups were deeply acidophilic staining, but coarsely granular in consistency and less refractile than in true hyaline change. The hyaline-like appearance was not uniform over any one patch, varying in its intensity of staining from one cell to another, and even from one part of a fiber to another part. Karyolysis in these cells

was not infrequently observed, and pyknosis was of relatively common occurrence. Irregularly shaped nuclei and occasionally empty ones indicated early stages of karyolysis. The other type of change encountered in the nodal muscle fibers was characterized by karyolysis of nuclei, vacuolization of cytoplasm, and loss of cell boundaries (Fig. 2). It was even more irregular in its distribution than the first type of structural alteration. Scattered areas showed almost complete myolysis of cells, while intervening areas were left relatively intact. Vacuolization was represented in some cells by numerous, nonstaining areas 3 to 4 μ in diameter. In other fibers the faded nucleus might be observed suspended freely in a completely vacuolated cell, in which only a thin strip of cortex remained; acidophilic degeneration of the karyoplasm



Fig. 2.—Sino-atrial nodal musculature in yellow fever. The heart rate of this animal (*M. rhesus* 12) was reduced to a third of its normal value during the course of yellow fever. The darker areas along the course of the fibers are areas of hyaline change. Vacuolization of fibers is also well shown. (Phloxin and azure B methylene blue.)

was a common nuclear change, and many nuclei were large, swollen, and hydropic in appearance. In what would seem to be the earlier stages of this process, the cytoplasm of the nodal cells appeared swollen, and composed of fine granules, which were palely staining and greatly dispersed. A fraying or fibrillation of the sarcolemma was a common finding. Cross striations in these fibers were usually lost, but in a few instances they were accentuated. In the later stages of this change, occasional cells appeared only in skeleton outline, with acidophilic cytoplasmic granules remaining interspersed between frayed myofibrillae. Cellular infiltrations were very rarely noted, and then only as sparse perivascular collections of lymphocytes. In some of the hearts examined

in this study actual necrosis of ganglion cells was observed. Many fields could be found in which two or more of these cells had been completely destroyed, with only the space previously occupied by the ganglion cell, or a cobweb-like network of palely staining cytoplasm, remaining. In the intermediate period leading to this complete lysis of nerve cells, the appearances of different cells suggested that both nucleus and cytoplasm had passed through successive stages. In the beginning the nucleus seemed to swell, at first somewhat disproportionately, its nuclear membrane becoming paler and less distinctly demarcated. At this stage the nucleolus could be observed as a palely staining oval disc colored a robin's egg blue by basophilic dyes and occupying



Fig. 3.—Sino-atrial nodal musculature in yellow fever. (*M. rhesus* 25.) Droplets of neutral fat, appearing as darkly shaded globules in the figure, are seen irregularly distributed in many fibers. (Sudan III and hematoxylin.)

the approximate center of the nucleus. About the nucleolus the chromatin structure first became altered both in form and in staining reactions. The normal appearance of a chromatin network and its grouping of particles became lost, and a greater or lesser aggregation of the latter, composed of pieces of chromatin grading down in size from a diameter one-eighth that of the nucleolus to the point of visibility, could be observed clustered together and apparently overlapping and fusing with each other. These particles gradually lost their affinity for basophilic dyes; they became colored by acidophilic stains, for the most part rather intensely. In later stages the aggregations of chromatin became chiefly grouped about the nucleolus, but smaller collections could be observed beneath the nuclear membrane; the intermediate nuclear zone was left

comparatively unoccupied. In the end, the nucleus frequently existed only as an oval vacuole containing loosely granular debris. Sometimes it appeared as a large oval disc, no longer possessing the sharply outlined border of the nuclear membrane but made up of dense, closely packed, coarsely granular, deeply staining, acidophilic, karyolytic debris. Concomitant changes in the cytoplasm were manifested by its substance becoming more coarsely granular. In some areas it acquired a purplish flush, losing its homogeneous mauve in phloxin and methylene blue preparations. Later there appeared areas of nonstaining or very pale staining protoplasm etching away its substance until the cytoplasm remained only as a vastly vacuolated cobweb-like structure. These changes which have been described in nodal muscle fiber and ganglion cell are the positive findings, the end picture of a varying degree of change which in different hearts progresses from a state which appears to deviate little from the normal. The nodal muscle fibers stained with Sudan III showed an irregular and patchy fatty degeneration (Fig. 3). While some fibers were very nearly free of fat, most cells contained a varying quantity. Many fibers presented large amounts of neutral fat in which the component droplets were for the most part of relatively large size; the size of these droplets ranged from 0.4 to 4 μ in diameter. Differing considerably in their size, the droplets varied much more in their distribution. They were usually largest and most numerous about the nucleus. The globules of fat tended to be arranged in parallel columns. Larger droplets appeared to have been formed by the coalescence of smaller ones. Some groups composed of twenty or thirty fibers were involved together in extreme fatty change in which 50 per cent or more of the total cell volume appeared to be occupied by neutral fat. The amount of fat was greatly in excess of the occasional dispersed fine granules which can sometimes be demonstrated normally in these fibers by the same technic. The ganglion cells showed occasional fat droplets in their cytoplasm.

The degenerative changes present in the nodal muscle fibers in the hearts of animals dead of yellow fever were at all times so marked that observers skilled in histopathology, examining unidentified microscopic preparation, were able to distinguish sections prepared from animals that had died from yellow fever from those obtained from control animals. Examined in this unprejudiced way, the sections which presented the most advanced lesions were found to have been taken from hearts which showed the most marked degrees of bradycardia during the course of the disease. In the nodal tissue from a monkey dying of a peritonitic infection there was a notable absence of degenerative changes.

2. Histological observations on the auricular muscle.

The alterations noted in the auricular muscle fibers were in no way different in character or degree from those observed in the specialized musculature of the node. When cut in cross-section the auricular mus-

cle fibers showed frequent perinuclear vacuolation and not uncommonly, loss of nuclei. Viewed in this way the cytoplasm of the cells presented a curious coarsely granular appearance because the cortices were composed of relatively large, deeply staining, loosely dispersed sarcoplasmic elements. In longitudinal section not only was perinuclear vacuolation well demonstrated, but vacuoles were frequently evident in other portions of the cell. The fiber itself usually exhibited a swollen hydropic appearance, and its outline was frequently less well demarcated than in normal tissues. Cross striations were rarely accentuated; more commonly they had become indistinct or quite lost. Fibrillation, unequal fraying, and disruption of the myofibrillae were commonly noted. When these processes reached extreme degrees in isolated cell groups, they

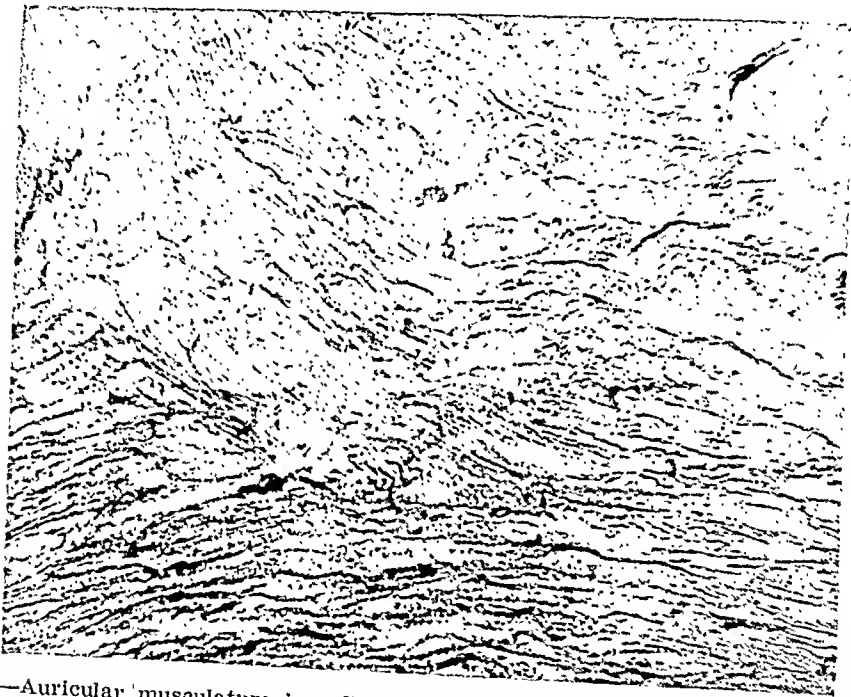


Fig. 4.—Auricular musculature in yellow fever. (*M. rhesus* 12.) Note vacuolization of protoplasm and karyolysis of nuclei. (Phloxin and azure B methylene blue.).

appeared as areas of myolysis. Sparse infiltrations of mononuclear leucocytes were only occasionally encountered. In addition to granular and vacuolar types of degeneration, a patchy hyaline-like change of the auricular fibers was frequently observed. In many instances this alteration affected whole cells but in its most typical form it was present as a transverse acidophilic "barring" of the longitudinally coursing muscle fibers. Such an appearance was imparted to these cells by an alternate patch-like accentuation of the acidophilic staining along the course of the fiber. Nuclear alterations were manifest in the common occurrence of pyknosis, while karyolysis was frequently observed in the areas of muscular degeneration and myolysis. In the cells of such areas the lysis of nuclei presented many and diverse forms, varying from swollen ones of distorted and irregular contour and watery ap-

pearance to nuclei disrupted and remaining only as acidophilic granular debris. In sections stained with hematoxylin and Sudan III, fat was observed to be present in relatively large quantities in the auricular muscle. The fatty degeneration, in common with the other types of cell injury, was irregular in its distribution from fiber to fiber and unequal in its quantity within each cell. Granular, vacuolar, and fatty degeneration with the rarer myolysis of cells are descriptive terms which represent the kind of picture which the lesion presented in different instances, and with the employment of various staining methods (Fig. 4).

3. *Histological observations on the auriculo-ventricular bundle.*

Sections of the crus commune of the auriculoventricular bundle stained with hematoxylin and eosin showed a patchy, hyaline-like change

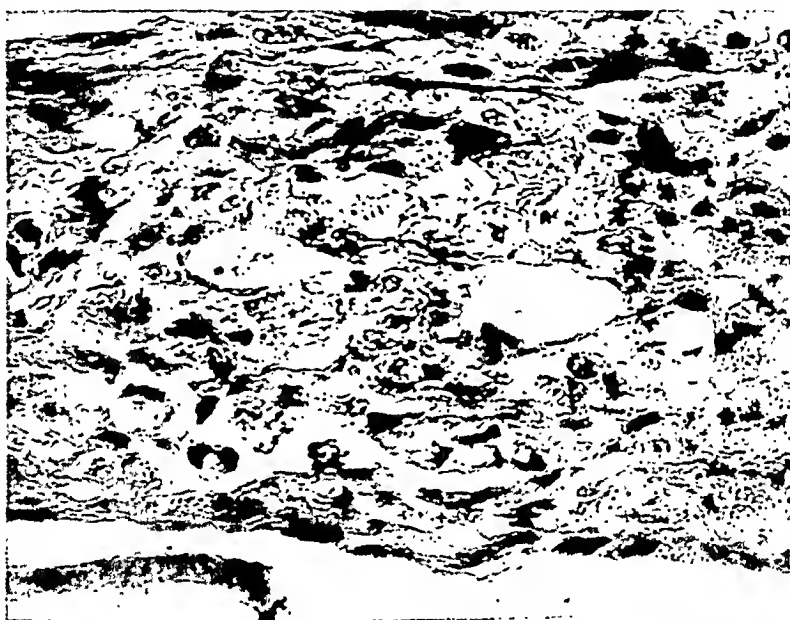


Fig. 5.—Auriculo-ventricular bundle in yellow fever. (*M. rhesus* 26.) Note vacuolar degeneration of protoplasm and karyolysis of nuclei. (Phloxin and azure B methylene blue.)

of many fibers. The cytoplasm of others was more coarsely granular than in normal control sections. Pyknosis was a common event, and karyolysis of nuclei was not infrequently encountered. More marked changes were occasionally met with in the bundle tissue. Once hemorrhage among the component cells was observed. When the fibers of the crus commune were studied in sections stained with iron hematoxylin and eosin, phloxin and azure B methylene blue, and Giemsa stain, the histopathological alterations became much more apparent than in sections stained with hematoxylin and eosin. Myolysis of small cell groups gave an appearance of etching away of portions of the bundle stem (Fig. 5). The nuclei of these degenerating cells frequently presented a swollen and hydropic structure, associated with fragmentation of the chromatin network. The staining qualities of the karyoplasm

became altered and more acidophilic in character with the progress of nuclear injury. Clumps of chromatin were conspicuous in these nuclei because of their size, bizarre form, and brilliantly acidophilic coloration. Frozen sections of the auriculo-ventricular bundle stained with Sudan III, demonstrated the presence of neutral fat in pathological amounts and distribution. The size of the droplets varied, but they were for the most part minute though numerous. The quantity of fatty change differed from area to area; in each cell the fat globules were usually most numerous about the nuclei. Sections of the auriculo-ventricular bundle prepared from healthy rhesus monkeys and treated by the same method of Sudan III staining, showed an absence of demonstrable fat in the specialized musculature. That special staining methods will

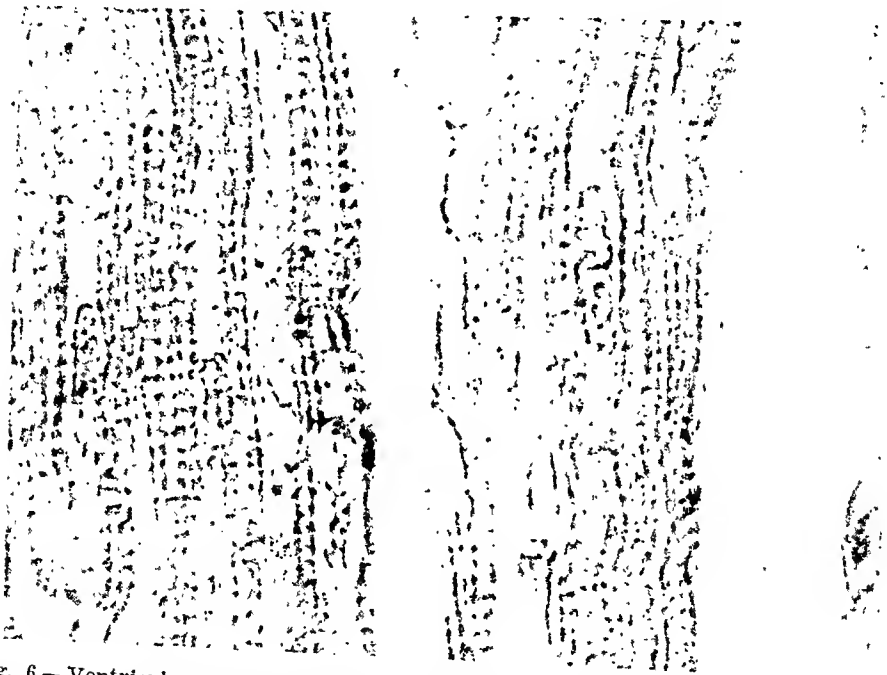


Fig. 6.—Ventricular musculature in yellow fever. (*M. rhesus* 13.) Note granular and vacuolar degeneration of protoplasm. This animal presented deformities of the ventricular electrocardiogram during the course of the disease. (Hematoxylin and eosin.)

permit the demonstration of fat in the normal auriculo-ventricular bundle⁴ and in the normal myocardium^{2, 3} has, however, been well demonstrated by Bullard. In the latter instance, the distribution is a much more uniform one than is encountered in disease.

4. *Histological observations upon the ventricular musculature.*

In sections of ventricular muscle both cross and longitudinal striations were frequently observed to be lost over wide areas. More rarely were these markings accentuated. The protoplasm of the fibers was coarsely granular, while perinuclear vacuolation was of common occurrence. The granular components of the cortices of these cells were rather widely dispersed beneath a swollen sarcolemma (Fig. 6). A patchy, glossy, hyaline appearance of portions of the fiber length, al-

ternating with more faintly staining areas, was frequently encountered. In many places cell outlines were lost, and nuclear degeneration forms were encountered in every field. Many nuclei were of irregular contour and pyknotic appearance. Not a few were seen to be swollen, surrounded by a thinned and stretched nuclear membrane, filled by a watery karyoplasm. A peculiar and rather definite type of karyolysis, more marked and elaborate in degree than anything of the sort observed in acute yellow atrophy or eclampsia, is worthy of mention. The train of events suggested by the process of nuclear destruction is that of a nucleus, at first swollen, of uniform or irregular contour, the chromatin network of which becomes first fragmented, then dispersed, and lastly clumped, at first basophilic, later amphichromatic, finally acidophilic and pale, the etching of its former self, transmogrified in rose-colored relief, in the perinuclear lacuna of a degenerated cell. Special fat staining of the ventricular muscle fibers demonstrated the occurrence of numerous globules, variable in number, patchy in distribution, linear in arrangement, and perinuclear in concentration, as had been observed in other parts of the myocardium.

DISCUSSION

On the basis of much physiological and anatomical knowledge there has developed a concept, fundamental to modern cardiology, that a bradycardia affecting the whole heart finds its origin in change of vagus nerve or sino-atrial node. In the experiments here recorded it has been shown that reduction of function in the vagal fibers to the heart by the administration of ether⁸ or by anesthesia with sodium iso-amyl-ethyl barbiturate,¹¹ or the abrogation of this function by bilateral section of the vagus nerves has no significant effect upon the slow heart action in experimental yellow fever.

The study of serial sections of the sino-atrial node in animals which presented a slow heart rate during the course of their infection with yellow fever has afforded us evidence of a positive nature. In this structure degeneration of the specialized nodal muscle fibers has been observed varying in degree and most marked in the cases presenting the slowest heart rates during life. Coexistent degenerative changes in the ganglion cells in contiguous or proximate relationship to this musculature, which might conceivably affect postganglionic vagal fibers, have also been noted. Although the proof cannot be absolute in the state of our present knowledge of the relation of myocardial injury to the evolution and determination of heart rate, it seems probable that the lesion of the sino-atrial tissues is responsible for, or closely related to, the production of the bradycardia of yellow fever.

Apart from the sino-atrial musculature, alterations in the auricular muscle proper have been noted by both physiological and histological methods during the course of experimental yellow fever. With the

changes observed in the auricular muscle by electrocardiographic methods may be correlated the alterations in this tissue revealed by histopathological studies. Pursuing a parallel course with the deformities of the P-wave, suggestive of a functional disturbance in the auricular muscle perhaps attended by a depressed function of the sino-atrial node, degenerative changes, varying in degree in different instances, have been manifest in the corresponding tissues. Occasionally small hemorrhages have been encountered in the auricular wall. In view of these concurrent alterations in form and function it seems reasonable to consider as a part of the myocardial degenerations of yellow fever an auricular degeneration which is associated with functional injury to atrial muscle, occasionally manifested by evident changes in the auricular electrocardiogram.

In the isolated auriculo-ventricular bundle we are afforded the opportunity of studying a portion of the myocardium which graphic, and histological methods enable us to delineate with a degree of accuracy unusual in biological investigation. Many observations during the past thirty years have definitely established the auriculo-ventricular bundle in the mammalian heart as the muscular link responsible for the conduction of the wave of excitation from auricle to ventricle. The lengthening of the P-R interval, moderate in degree, which has been observed with considerable constancy in the electrocardiographic records of experimental yellow fever in the monkey, may be considered as a sign of impairment of function in the auriculo-ventricular bundle. The histopathological examination of the junctional tissues presenting such evidence of functional impairment has demonstrated the presence of clearly demarcated degenerative changes. The pathological basis of impaired conduction has been found in a degeneration of the muscular fibers of the auriculo-ventricular bundle, which thus altered by the disease may present the appearances of granular, fatty, hyaline, vacuolar, or myolytic change.

The occurrence of degenerative lesions in the ventricular musculature in experimental yellow fever becomes an important consideration in view of the fact that functional disturbances in this tissue during the course of the disease were provocative of deformity of the R-T segment and inversion and deformity of the T-wave. This evidence, taken in conjunction with our knowledge of the existence of similar disturbances in rheumatic fever, diphtheria, influenza, infarction of the ventricle, and alkaloidal and other poisoning of the myocardium suggests the importance of these deformities of the ventricular electrocardiogram as evidence of injury to ventricular muscle. The injury may be transient, the effect fleeting, and the damage temporary.

SUMMARY

The histopathological examination of the myocardial tissues of animals dead of experimental yellow fever has demonstrated the existence of

well-marked degenerative changes, presenting protean characters, in the musculature of sino-atrial node, auricle, auriculo-ventricular bundle, and ventricle. The impression has not been obtained that the degree of degeneration is greater in one part of the myocardium than in another part; nevertheless, the advantages of considering each part separately from the pathological standpoint are as obvious as those of considering the various portions individually as anatomical and physiological entities. Fatty degeneration of the muscular fibers of the heart, varying in degree and patchy and irregular in distribution, has been a constant finding in experimental yellow fever. Granular degeneration of the myocardium has been of equally common occurrence. In other instances, but in most cases in lesser degrees, hyaline and vacuolar types of muscle degeneration have been encountered. A characteristic but not a constant finding, recalling a similar one observed in diphtheritic hearts, has been a patchy myolysis of isolated muscle-fiber groups. Occasional small petechial hemorrhages have been observed scattered through the myocardium. Only rarely have cellular infiltrations been met with as small numbers of lymphocytes and endothelial leucocytes clustered about the smaller blood vessels. In the rarer instances, when these inflammatory cells have been observed, it is thought that the degenerating tissue has afforded the chemotactic stimulus for their response. The lesions of the myocardium, like those in the parenchymal tissues of other organs, are primarily degenerative in character. The degenerative lesions of the myocardium in yellow fever represent a well-marked structural basis for the occurrence of functional disturbances in its various parts.

The author wishes to express his thanks to Dr. D. A. Irwin, who took the microphotographs here presented, and to Dr. W. A. Sawyer and Dr. S. F. Kitchen who kindly secured many specimens for him. The aid, advice, and generous concession of time and knowledge afforded the writer by Professor Oskar Klotz have been of the greatest assistance in the performance of the work.

REFERENCES

1. Aitken, Connal, Gray, and Smith: *Tr. Roy. Soc. Trop. Med. & Hyg.* 20: 166 1926.
2. Bullard: *Anat. Rec.* 8: 12, 1912.
3. Bullard: *Am. J. Anat.* 19: 1, 1916.
4. Bullard: *Johns Hopkins Hosp. Repts.* 18: 329, 1919.
5. Cannell: *Am. J. Path.* 4: 431, 1928.
6. Elliott: *Arch. Int. Med.* 25: 174, 1920.
7. Fialho: *Arch. de hyg.* 3: 37, 1929.
8. Gold, Gryzwaecz, and Nowicki: *AM. HEART J.* 4: 336, 1928-29.
9. Hudson: *Am. J. Path.* 4: 407, 1928.
10. Klotz: *De Lamar Lectures*, 1927-28, Baltimore, 1928, Williams & Wilkins Co.
11. Lieb and Mulinos: *Proc. Soc. Exper. Biol. & Med.* 26: 709, 1929.
12. Marchoux and Simond: *Ann. d. l'Inst. Pasteur.* 20: 104, 1906.
13. Otto: *Handbuch der Tropenkrankheiten*, edited by Carl Mense, Vol. 3, p. 554. J. A. Barth, Leipzig.
14. Otto and Neumann: *Ztschr. f. Hyg. u. Infektionskr.* 51: 357, 1905.
15. Rocha Lima: *Verhandl. d. deutsch. pathol. Gesellsch.* 15: 163, 1912.
16. Seidelin: *Yellow Fever Bur. Bull.* 1: 173, 1911-12.
17. Sodre and Couto: *Specielle Pathologie und Therapie*, edited by Nothnagel, Vol. 5, part 2, chap. 3, p. 104, Vienna, 1901, Alfred Hölde.

CHANGE IN THE SIZE OF THE HEART IN SEVERE ANEMIA

WITH REPORT OF A CASE

DAVID BALL, M.D.

NEW YORK, N. Y.

ENLARGEMENT of the heart and the presence of systolic murmurs, in cases of severe anemia, have been recognized and well known for many years. Most of the observations are based upon clinical and post-mortem findings in cases of pernicious anemia.

The character of the murmurs may differ in no way from those heard in mitral disease of rheumatic or atherosclerotic origin. The severe anemias of rheumatic infection are well recognized. The problem then confronts the clinician as to whether or not the cardiac condition is dependent upon the anemia or is dependent upon true structural changes. If a surgical procedure is contemplated, the problem becomes acute. The following case shows how great this difficulty may be and illustrates how an enlarged heart, with apical and basal murmurs simulating organic valvular disease, may return to normal with relief of the anemia.

After an extensive search of the literature, I have been unable to find a case, proved roentgenologically, of definite enlargement of the heart in severe secondary anemia with a subsequent decrease in size associated with a return of the blood picture to normal. This report is based upon such a case.

CASE REPORT

E. K., a woman, aged 35 years, sought medical aid on February 25, 1930, complaining chiefly of profound weakness and dyspnea on slight exertion. She had been married for twelve years and had three children, the youngest of whom was four years old. Her past history was entirely negative. There was no history of rheumatic fever, chorea, tonsillitis, or joint pains. She was perfectly well until six months before when she began to bleed profusely with her menstrual periods. Menses remained regular and the severe menorrhagia continued each month. She gradually lost strength and about fifteen pounds in weight, and for two to three weeks noticed increasing dyspnea on exertion. One week before she had felt a "lump" in her lower abdomen.

Physical examination revealed a fairly well-nourished adult female with marked pallor of the conjunctivae, lips, and skin. She did not appear acutely ill. The heart was enlarged to both the right and the left on percussion. A loud, blowing, systolic murmur was present all over the precordium, but was heard best in the third and fourth interspaces about an inch to the left of the sternum. No diastolic murmur could be heard. The second pulmonic sound was louder than the second aortic sound. Blood pressure was 140/80 mm. The rest of the physical examination was negative except for a hard, nodular mass rising out of the pelvis and reaching to within 6 cm. of the umbilicus.

Teleroentgenogram (Fig. 1A) showed a generalized enlargement of the heart to the left and right and a moderate straightening of the left border with slight bulging in the region of the pulmonary conus, the picture of an advanced mitral lesion. The total transverse diameter of the heart (13.3 cm.) was greater than half of the transverse diameter of the thorax (26.0 cm.).

Electrocardiogram (Fig. 2A) showed a normal sinus rhythm with a left ventricular preponderance. On February 28, 1930, the hemoglobin was 35 per cent and the red blood cell count 2,500,000 per cubic millimeter. The white blood cells numbered 9000 per cubic millimeter with 68 per cent polymorphonuclears and 32 per cent lymphocytes. The patient was hospitalized and carefully observed. She

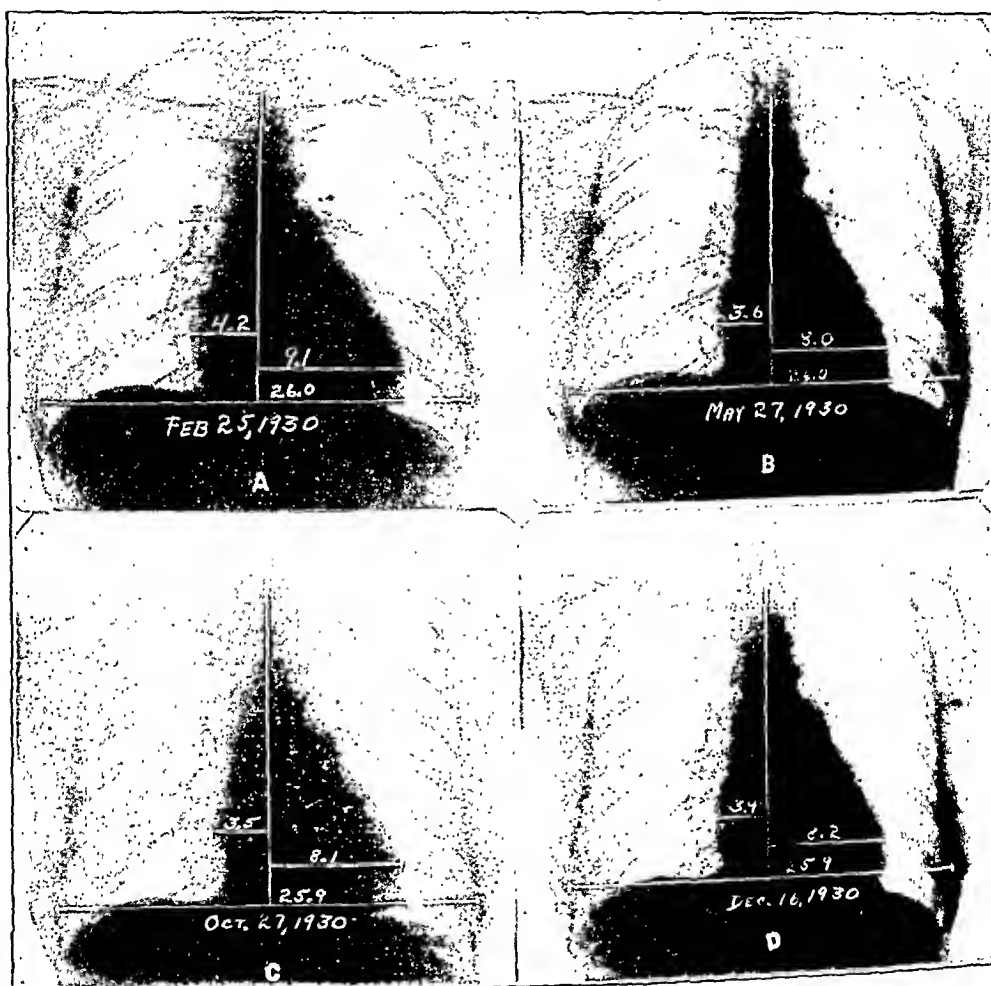


Fig. 1-A.—Note enlargement of the heart to right and left with typical "mitral contour." Total transverse diameter of heart 13.3 cm.

Fig. 1-B.—Decrease in size of right and left heart. Total transverse diameter of heart 11.6 cm. Decrease of 1.7 cm.

Fig. 1-C.—Same size and shape of heart as in Fig. 1-B. Total transverse diameter of heart 11.6 cm.

Fig. 1-D.—Same as Fig. 1-C. Total transverse diameter of heart 11.6 cm.

was menstruating profusely at the time and continued so until March 6, 1930. The temperature remained normal. The hemoglobin was estimated daily and varied between 35 per cent and 41 per cent. The cardiac picture remained unchanged. It was decided that the severe secondary anemia due to bleeding fibroids was probably the cause of the cardiac findings, and that hysterectomy had to be done to remove the cause and to stop the progression of the severe anemia in an attempt to pre-

vent further cardiac damage. On March 8, 1930, the patient was given a direct transfusion of 500 c.c. of blood, and this was followed by a slight rise in temperature. Hemoglobin the next day had risen to 62 per cent and by March 16, 1930, had reached 72 per cent, and the red blood cells numbered 3,900,000 per cubic millimeter. The next day the patient was operated upon by Dr. Robert T. Frank. A large fibromyoma of the uterus was found. A supravaginal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The patient had an uneventful postoperative course. The hemoglobin ranged between 70 and 74 per cent. The patient left the hospital on April 3, 1930. The heart appeared definitely smaller on percussion, and the loud systolic murmur previously heard was barely audible.

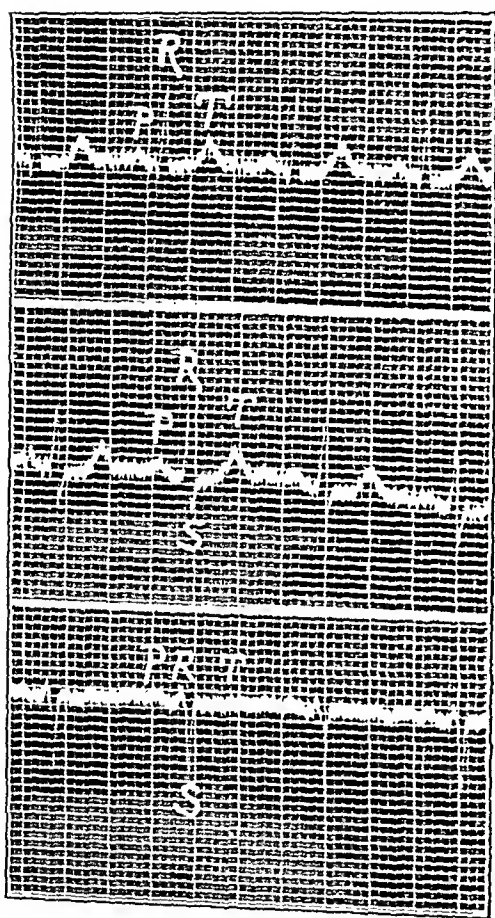


Fig. 2-A.

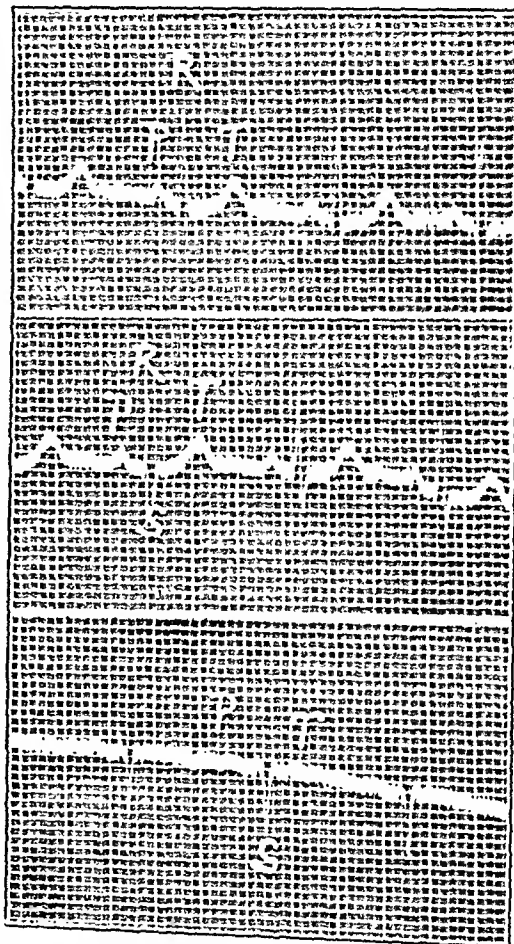


Fig. 2-B.

Fig. 2.—A, Taken February 25, 1930. Left ventricular preponderance. B, Taken December 16, 1930. Left ventricular preponderance, slightly less than A.

Teleroentgenogram (Fig. 1B) taken on May 27, 1930, three months after the first one, showed a marked decrease in the size of the heart with only slight evidence of "mitralization" of the left border. The total transverse diameter of the heart was 1.7 centimeters less, this diminution involving both the right and left sides of the heart. On examination at this time, the heart sounds were all normal and a faint, soft systolic murmur could be heard at the apex. On held inspiration the murmur disappeared entirely. The patient was symptom free.

A third teleroentgenogram (Fig. 1C) taken on October 27, 1930, was the same as the previous one, with practically no evidence of mitralization. The hemoglobin at this time was 95 per cent. Heart sounds were normal, and no murmurs could

be heard even after exercise. The heart at this time, both clinically and radiographically did not reveal any evidence of organic or functional disease.

A fourth teleroentgenogram (Fig. 1D) taken on December 16, 1930, was the same as the previous one.

An electrocardiogram taken at this time (Fig. 2B) was practically the same as the original one except that the left ventricular preponderance was slightly less marked.

The patient was first seen in consultation. Because of the marked subjective complaints and the cardiac findings, it was felt that the patient probably had an organic valvular defect and that the symptoms were aggravated by the severe anemia. The subsequent course of the case proves rather conclusively that the change in circulatory dynamics was due to the anemia and not to structural changes in the heart.

The earliest observations on the behavior of the heart in anemia deal with cases of "chlorotic" individuals. Irvine¹ in 1877, Barrs² in 1891, and Hersman³ in 1893 described murmurs that disappeared with a cure of the anemia. Gautier⁴ in 1899 found cardiac enlargement by percussion in twenty out of twenty-two cases of chlorosis. Kraus⁵ in a review of forty-seven cases of pernicious anemia found cardiac dilatation in thirty on percussion. Goldstein and Boas⁶ found that cardiac dilatation as well as hypertrophy occurred not only in pernicious anemia, but also in severe secondary anemia. Lewis and Drury⁷ state that the heart can dilate because of an insufficient blood supply to it. Lüdke and Schüller⁸ produced enlargement of the heart in dogs, experimentally by rendering the animals anemic. Fahr and Rhonzone⁹ describe the circulatory dynamics in severe anemia showing how the increased work of the heart produces ventricular hypertrophy.

The above observations and the clinical course seem to support the belief that the case herein reported was probably almost entirely in the nature of dilatation. The total transverse diameter of the heart decreased almost 2 cm. in three months. Clinically this change was observed within one month, obviously too short an interval for hypertrophy to disappear.

SUMMARY

A case of severe anemia due to bleeding fibroids is presented, showing that the dilated heart of anemia may become smaller in size and normal in shape, as proved by teleroentgenograms, very soon after the cause of the anemia is checked and the blood picture returns to normal. Cardiac enlargement is a frequent finding in patients suffering with severe anemias. Roentgenologically, the enlarged heart of anemia often cannot be differentiated from the picture of organic valvular disease. The enlarged heart found in severe anemias may decrease in size when the anemia is cured. The cardiac murmurs heard in severe anemias can disappear entirely when the anemia is

cured. The finding of an enlarged heart together with the typical physical signs and x-ray picture of organic valvular disease in a patient with a severe anemia, does not in itself indicate organic cardiac disease.

I wish to express my appreciation to Dr. Marcus A. Rothschild for his helpful suggestions.

REFERENCES

1. Irvine, P.: *Lancet* 1: 837, 1877.
2. Barrs, A. G.: Cardiac Bruits of Chlorosis, *Am. J. Med. Sc.* 102: 347, 1891.
3. Hersman, C. F.: Temporary Mitral Insufficiency in Anemic Conditions. *Internat. M. Mag., Phila.* 2: 341, 1893.
4. Gautier, E.: Ueber die morphologischen Veränderungen des Herzens bei der Chlorose auf Grund klinischer Beobachtungen. *Deutsches Arch. f. klin. Med.* 62: 120, 1899.
5. Kraus, F.: Die klinische Bedeutung der fettigen Degeneration des Herzmuskels schwer anämischer Individuen. *Berl. klin. Wchnschr.* 42: 111, 1905.
6. Goldstein, B., and Boas, E. P.: Functional Diastolic Murmurs and Cardiac Enlargement in Severe Anemias. *Arch. Int. Med.* 39: 226, 1927.
7. Lewis, T., and Drury, A. N.: Observations Relating to Arteriovenous Aneurysm, *Heart* 10: 301, 1923.
8. Lüdke, H., and Schüller, L.: Ueber die Wirkung experimenteller Anämien auf die Herzgrösse, *Deutsches Arch. f. klin. Med.* 101: 512, 1910.
9. Fahr, G. E., and Rhonzone, E.: Circulatory Compensation for Deficient Oxygen Carrying Capacity of the Blood in Severe Anemias, *Arch. Int. Med.* 29: 331, 1922.

THE ELECTROCARDIOGRAPHIC CHANGES IN MYOCARDIAL ISCHEMIA*

H. S. FEIL, M.D., L. N. KATZ, M.D., R. A. MOORE, M.D., AND
R. W. SCOTT, M.D.
CLEVELAND, OHIO

I. THE EFFECTS OF LIGATION OF THE LEFT DESCENDING CORONARY ARTERY WITH AND WITHOUT OCCLUSION OF THE INFERIOR VENA CAVA

IN PREVIOUS papers^{1, 2} we reported our observations on the electrocardiographic changes in experimental and clinical pericardial effusion. Deformities in the R-T complex similar to those seen in recent myocardial infarction were observed. These changes were ascribed to myocardial ischemia resulting from increased hydrostatic pressure in the pericardial sac. The present work was undertaken to study further the effects of acute experimental myocardial ischemia on the electrocardiogram. For this purpose the ramus descendens of the left coronary artery alone was tied. Further reduction in the blood supply to the heart was induced by occlusion of the vena cava inferior.

Experimental occlusion of the coronary arteries is known to cause changes in the R-T complex.^{3, 4, 5, 6, 7} Recently Gruber⁸ found that generalized anoxemia caused electrocardiographic changes which were exaggerated by drugs which presumably constrict the coronary arteries.

METHOD

Twenty-nine dogs ranging in weight from fourteen to thirty-eight kilograms were used. The animals were anesthetized with morphine and barbitol. The chest was opened and artificial respiration instituted. The pericardium was split and attached to the chest wall to form a hammock for the heart. In this way a reasonably constant position of the heart was maintained throughout the experiment. Under the inferior vena cava a half-inch tape was placed, which when pulled taut occluded the vessel. The ramus descendens of the coronary artery was freed from its sheath, and a waxed silk thread was placed under it. The vessel was ligated at varying levels (1 to 4.5 cm.) from the mouth of the left coronary artery. In a few preliminary experiments the coronary vein was occluded in the tie. After a variable period following the coronary tie (9 to 58 minutes) the inferior vena cava was temporarily occluded for from 3 to 5 minutes.

Electrocardiograms were taken, using the three standard leads, immediately before (control), at various stages after the coronary tie, and during the occlusion of the inferior vena cava. In most of the experiments a continuous mean blood pressure tracing was recorded. At the end of each experiment the heart was

*From the Departments of Physiology and Medicine and the Institute of Pathology, Western Reserve University Medical School.

Read in abstract before the Association of American Physicians, Atlantic City, May 3, 1930.

injected by Gross's barium sulphate method.⁹ This procedure afforded a check on the completeness of the experimental tie and showed the extent of the anastomosis in the area supplied by the occluded vessel.

RESULTS

The principal effects on the electrocardiogram of ligation of the ramus descendens of the left coronary artery may be considered under three headings as follows:

I. The Effect on the Cardiac Mechanism.—Twenty-six successful coronary ligations were made. In eight of these death as a result of ventricular fibrillation occurred within five minutes. Six animals developed ventricular fibrillation within eleven to seventeen minutes; three developed dilatation and fibrillation of the ventricles (seventeen, forty, and forty-six minutes, respectively after the coronary tie) as a result of manipulation. The remainder, nine in number, were sacrificed from thirty-eight to sixty-eight minutes after the coronary tie. In other words, ventricular fibrillation directly attributable to coronary occlusion occurred in approximately 54 per cent of our animals within the first hour.

In one instance a record was obtained at the onset of ventricular fibrillation (Fig. 1). After a few premature ventricular beats, the last one of which is shown in the figure, a run of ventricular tachycardia was inaugurated by a premature ventricular beat and terminated by ventricular fibrillation.

Analysis of our curves showed no relation between the presence of ventricular fibrillation and the level at which the artery was tied, the abundance of anastomosis, or the weight of the dogs. In most instances the animals that developed ventricular fibrillation had premature contractions and paroxysmal tachycardia as well.

Ventricular premature contractions were common sequelae, occurring in sixteen animals. In half the cases the premature contractions arose from several foci. Short and long runs of ventricular paroxysmal tachycardia were also common (occurring in ten animals). In several instances the paroxysmal tachycardia arose from several foci. In one case, the origin was auricular. Sinus bradycardia developed in three animals and sinus tachycardia in two others. In four animals no change of mechanism occurred.

II. The Effect on the Mean Blood Pressure.—Ligature of the coronary artery led to surprisingly small changes in the mean blood pressure. In only six out of nineteen animals in which it was recorded, did the blood pressure drop permanently following the coronary occlusion, and this drop was only from 5 to 20 mm. Hg. In four others there was a temporary drop followed by a return to normal or actually to a level higher than normal (10 mm. Hg. in one and 25 mm. Hg. in the other). In four animals no change in blood pressure occurred. In five the blood pressure rose from 10 to 30 mm. Hg. following the coronary

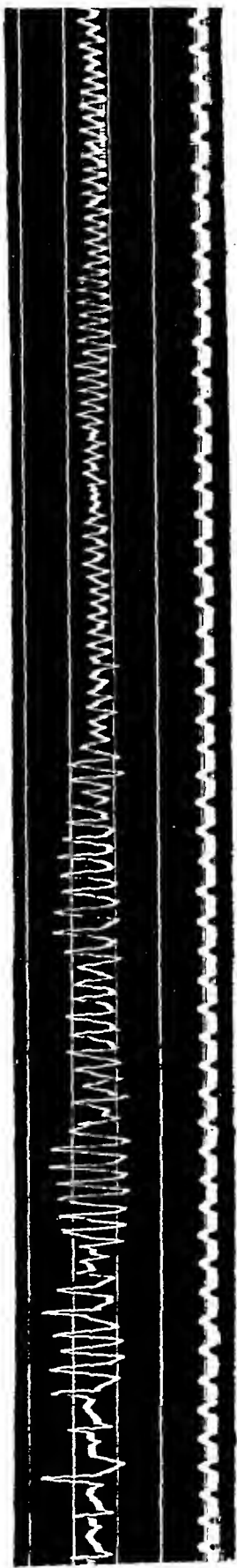


Fig. 1.—Electrocardiogram, Lead II, showing the onset of ventricular fibrillation. Time 0.2 sec.

tie; in one of these, however, the pressure later dropped to below normal. In every instance a decided drop in blood pressure occurred with premature contractions and paroxysmal tachycardia. The magnitude of the drop varied from 20 to 40 mm. of Hg.

III. The Effect on the R-T Segment and the T-wave of the Electrocardiogram.—Occlusion of the left descending coronary artery alone caused only slight alteration in the R-T segment, provided the mechanism remained normal. The only change that did occur in most of the cases was in the T-wave. This consisted in an increase in the amplitude of an upright T (c.f. segments 1, 3, and 7 in Fig. 2), a decrease in the amplitude of an inverted T (c.f. segments 1, 3, 5, 8, in

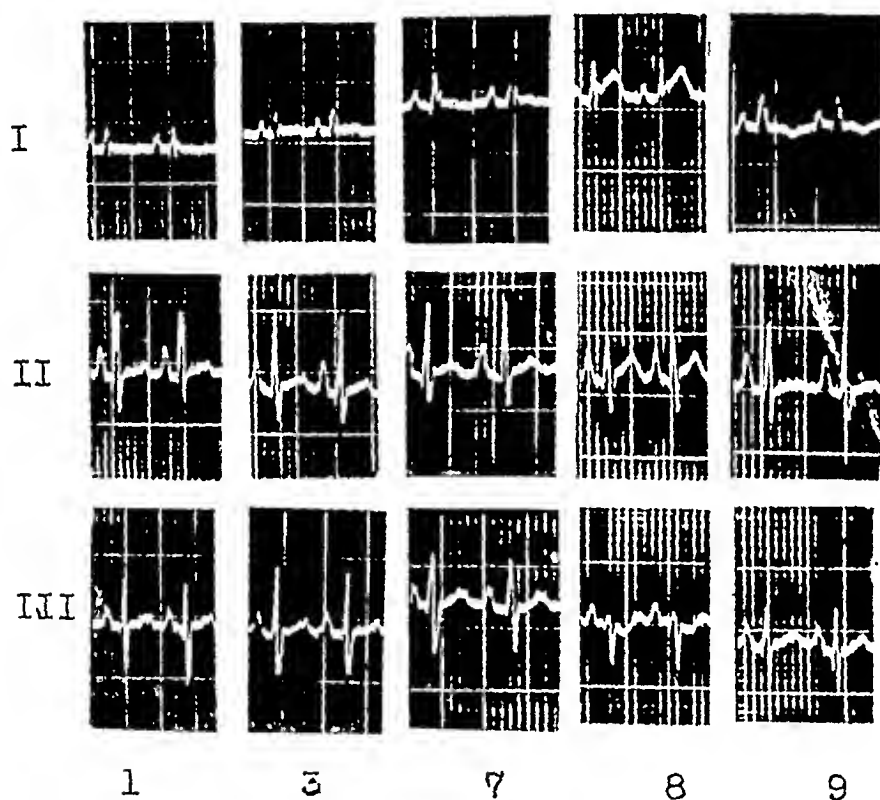


Fig. 2.—Typical segments of experiment on Dog 16.

- (1) Control.
- (3) Seven minutes after left coronary was tied.
- (7) Forty minutes after left coronary was tied.
- (8) Forty-five minutes after left coronary was tied and five minutes after inferior vena cava tie.
- (9) Fifty minutes after left coronary was tied and five minutes after vena cava tie was released.

Fig. 3), and the transformation of a small inverted T into a small upright one (c.f. segments 1 and 2 in Fig. 5).

In two control animals ligatures were placed under the coronary arteries but not tied. This procedure alone caused slight directional change in the T-wave. It would seem, therefore, that little significance can be attached to the minor changes in the T-wave after coronary ligation.

In two animals in which the vein as well as the artery was tied,

slight characteristic changes in the R-T segment were present with normal mechanism.

The appearance of frequent premature contractions or of paroxysmal tachycardia was followed in practically all cases by characteristic

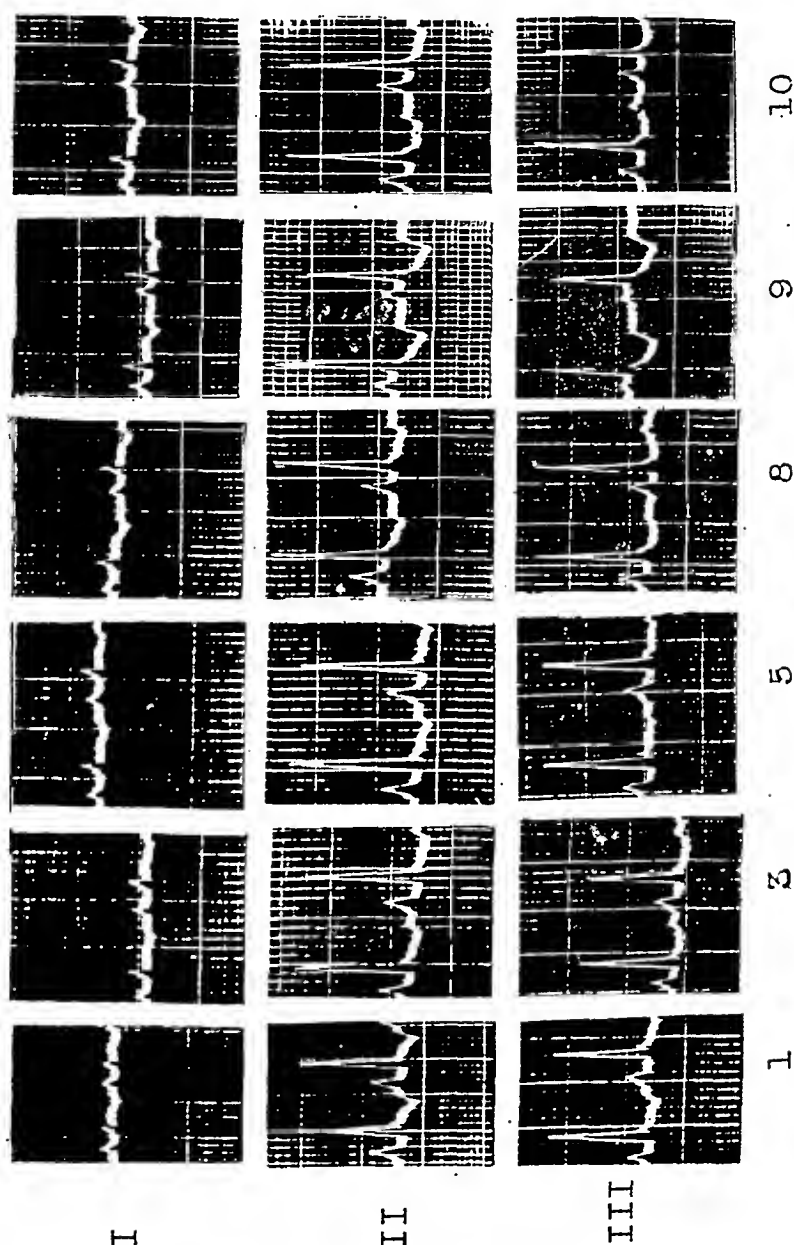


Fig. 3.—Typical segments of experiment on Dog 21.

- (1) Control.
- (3) Six minutes after left coronary was tied.
- (5) Thirty minutes after left coronary was tied.
- (8) Forty-two minutes after left coronary was tied.
- (9) Forty-seven minutes after left coronary was tied and five minutes after inferior vena cava tie.
- (10) Fifty-two minutes after left coronary was tied and five minutes after inferior vena cava tie was released.

R-T deviations which tended to disappear with the restoration of a normal mechanism. This is well shown in Figs. 4, 5 and 6. Dog 26, whose record is shown in Fig. 4, developed frequent premature con-

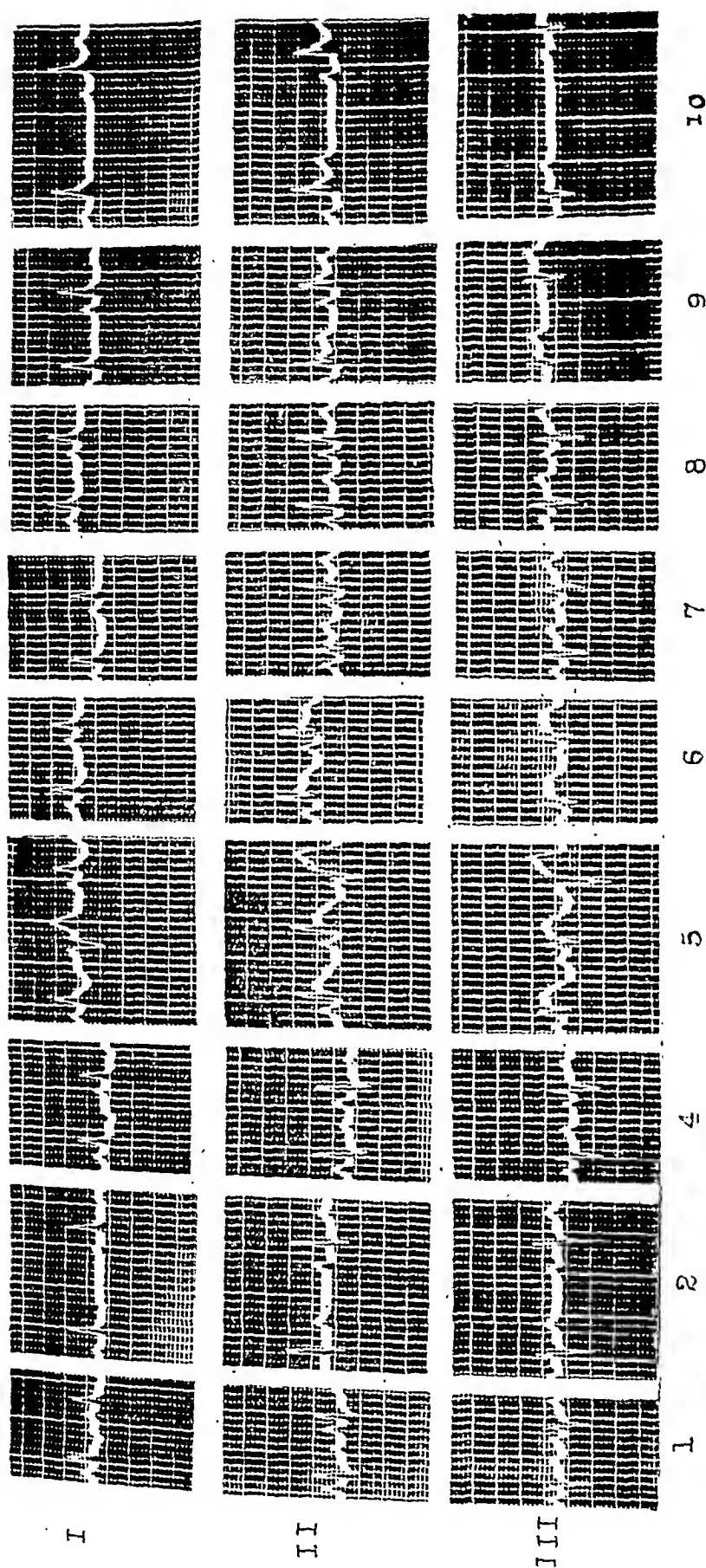


Fig. 4.—Typical segments of experiment on Dog 26.

- (1) Control.
- (2) Inferior vena cava tied for five minutes.
- (3) Sixteen minutes after inferior vena cava tie was released.
- (4) Two minutes after left coronary was tied.
- (5) Ten minutes after left coronary was tied.
- (6) Twenty minutes after left coronary was tied.
- (7) Thirty minutes after left coronary was tied.
- (8) Thirty-four minutes after left coronary was tied and four minutes after inferior vena cava tie.
- (9) Thirty-nine minutes after left coronary was tied and five minutes after inferior vena cava tie was released.
- (10)

tractions occurring singly and in short runs and coming from several foci. This irregularity started about a minute after the coronary was tied, reached its maximum two minutes later, and disappeared within ten minutes. (See segment 5 of Fig. 4.) The positive S-T segment in Leads II and III is apparent, as is the short positive S-T followed by a negative T in lead I. These abnormalities are in sharp contrast to the normal configurations of the electrocardiogram in segment 4, the control. Segments 6, 7 and 8 of Fig. 4 show the return of the electrocardiogram to normal in a period of thirty minutes. Segment 8 differs from the control segment 4 only in that it has a larger T in Leads

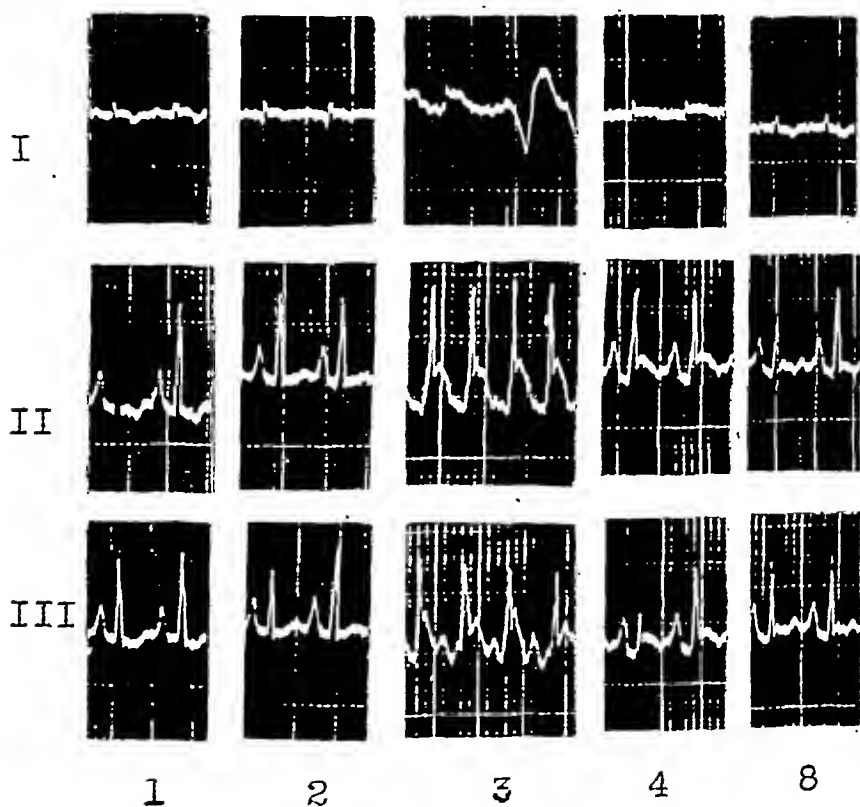


Fig. 5.—Typical segments of experiment on Dog 18.

- (1) Control.
- (2) Four minutes after left coronary was tied.
- (3) One minute after left coronary was tied.
Paroxysmal tachycardia stopped by stimulation of peripheral left vagus.
- (4) Two minutes later and eleven minutes after left coronary was tied.
- (8) Thirty-nine minutes after left coronary was tied.

II and III with a slight slurring of the descending limb of R in Lead I. Dog eighteen whose record is shown in Fig. 5, developed auricular paroxysmal tachycardia, interrupted by short runs of ventricular tachycardia. This irregularity was interrupted and a normal mechanism restored by stimulating the peripheral end of the left vagus with a faradic current. Except for the T-wave becoming upright, no change occurred in the electrocardiogram four minutes after the coronary ligation (c.f. segments 1 and 2). During the tachycardia, segment 3, a high take-off of the S-T segment is seen. This persists in a milder

form two minutes after the tachycardia was interrupted, segment 4, and has practically disappeared thirty-nine minutes later, segment 8. Dog 30, whose record is shown in Fig. 6, developed ventricular premature contractions from several foci which on occasion occurred in short runs following the ligation of the coronary artery. Segments 5, 6, and 7 show the high take-off of the S-T segment in the normal sinus beats between the premature contractions.

It appears, therefore, that an abnormal cardiac mechanism (premature contractions and tachycardia) is a factor in myocardial ischemia. In hearts developing an abnormal mechanism following coronary ligation, positive R-T deviations occurred. On the other hand, no such changes were seen in hearts which continued to beat normally following coronary ligation. The intervention of a cardiac irregularity in a heart already partially deprived of its blood supply, acts as an added insult by further impairing the coronary flow.

IV. The Effect of Inferior Vena Cava Ligation.—In eleven animals the inferior vena cava was temporarily occluded twenty times at various periods after the coronary ligation (nine to fifty-eight minutes). The occlusion lasted from three to five minutes. In every case the mean blood pressure fell to a level ranging from 45 to 60 mm. Hg., with one exception when it fell to 70 mm. Hg. This represented a drop in pressure ranging from 40 to 80 mm. Hg.

The most common change in mechanism following the ligation of the vena cava was a sinus bradycardia (17 experiments out of 20). In one animal in which the inferior vena cava tie was made three times no change in mechanism occurred. In one experiment complete heart-block developed. The effect of the inferior vena cava tie on premature contractions was variable. The records of one experiment show (Fig. 6) that the premature contractions present before the vena cava tie disappeared following the tie. In one experiment the cava ligation induced ventricular premature contractions, while in two other instances premature contractions persisted after cava ligation.

As a rule characteristic R-T deviations appeared after ligation of the inferior vena cava. For example, in Dog 16, in which ligation of the coronary artery had no effect on the S-T segment (e.g. Fig. 2 segments 1, 3 and 7), occlusion of the inferior vena cava for five minutes produced a positive S-T take-off in Leads I and II and a negative take-off in Lead III. These changes disappeared again five minutes after release of the ligature on the cava. Fig. 3 illustrates a similar result in Dog 21. In this animal no change in the S-T segment occurred following coronary tie, i.e., segments 3, 5 and 8, until the inferior vena cava was ligated for five minutes (segment 9) when a marked negative S-T segment developed in Leads II and III which tended to disappear five minutes after releasing the caval tie (segment 10). In Fig. 4, is shown the gradual return to normal of the

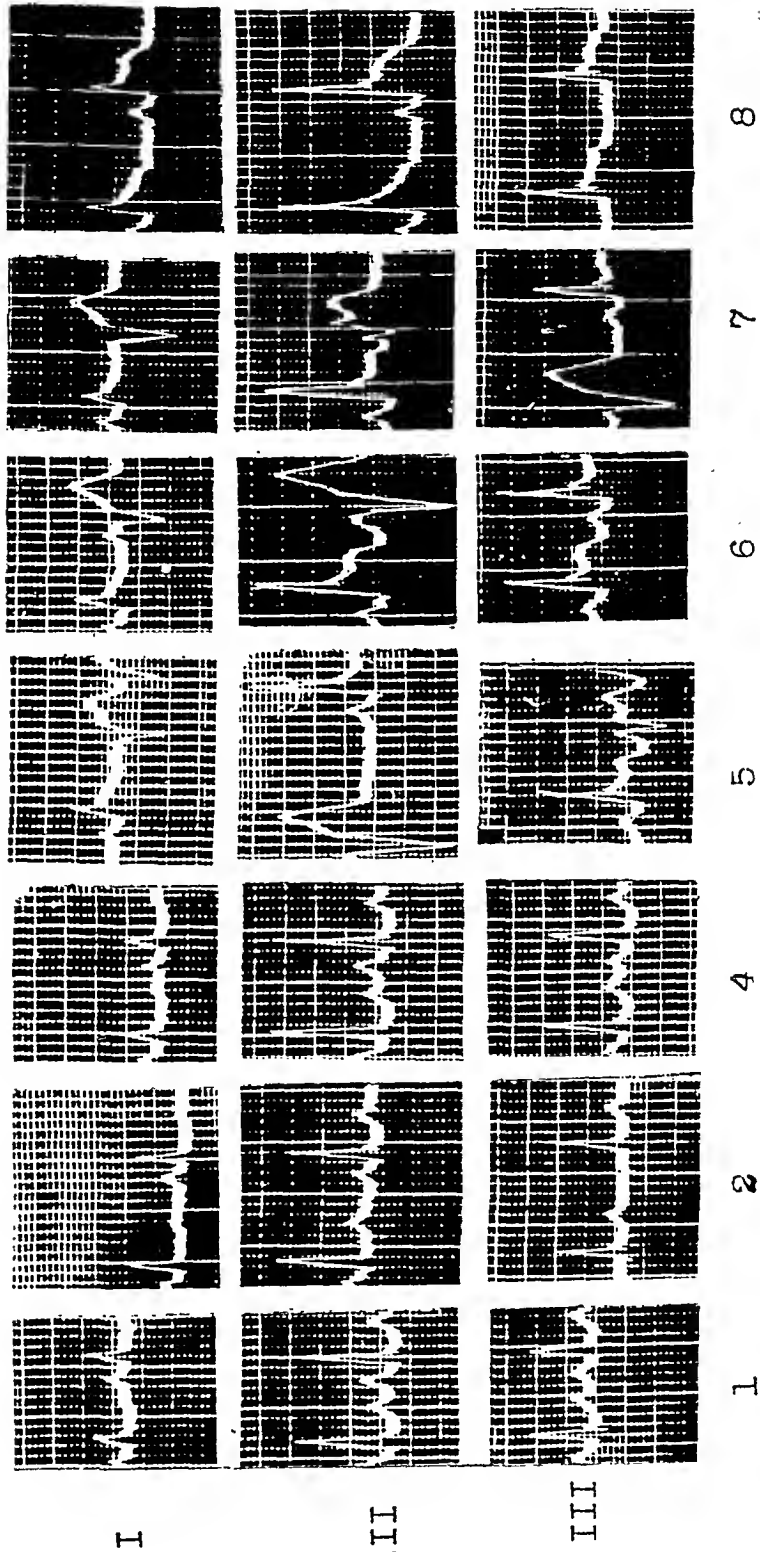


Fig. 6.—Typical segments of experiment on Dog 30.

- (1) Control.
- (2) Inferior vena cava tied for five minutes.
- (3) Twelve minutes after inferior vena cava tie was released.
- (4) Two minutes after left coronary was tied.
- (5) Five minutes after left coronary was tied.
- (6) Eight minutes after left coronary was tied.
- (7) Thirteen minutes after left coronary was tied and five minutes after inferior vena cava tie.
- (8)

S-T deviation following a coronary tie which appears in segment 5 associated with frequent premature contractions (segments 6, 7, 8). After ligation of the inferior vena cava the S-T abnormality reappears (c.f. segments 9 and 10). The effect of occlusion of the inferior vena cava for five minutes in augmenting the S-T abnormality produced by frequent premature contractions is shown in Fig. 6 (c.f. segments 7 and 8). In the majority of instances the S-T deviation caused by ligation of the inferior vena cava tended to disappear when the ligation was released (e.g. segment 9, Fig. 2 and segment 10, Fig. 3).

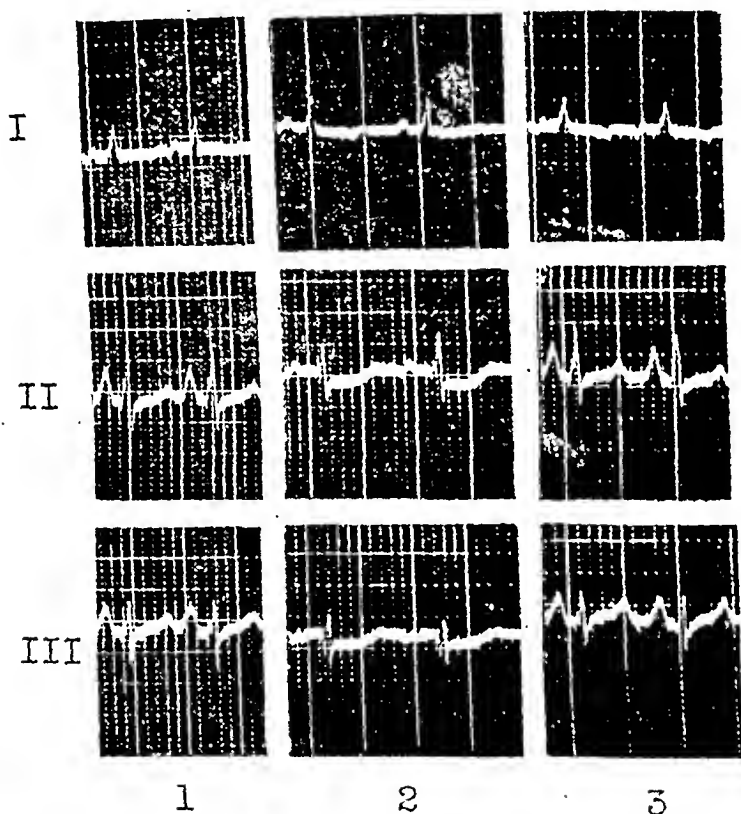


Fig. 7.—Typical segments of control experiment on Dog 31.

- (1) Control.
- (2) Inferior vena cava tied for five minutes.
- (3) Five minutes after inferior vena cava tie was released.

Control experiments were performed. In ten animals the inferior vena cava was tied while the coronary arterial circulation was uninterrupted. Sinus bradycardia occurred in nine of these animals during the cava occlusion. In the other instance sinus tachycardia developed. The mean blood pressure was reduced to a level of 50 to 70 mm. Hg. which indicated a drop from 45 to 90 mm. Hg. The changes in blood pressure in these controls are therefore of the same order as in the other experiments. No changes were present in the S-T segment in most of the controls (e.g. segments 1, 2 and 4 of Fig. 4 and segments 1, 2 and 4 of Fig. 6). In three animals the S-T segment became slightly negative (0.5 to 1 mm. in one or two leads). In

only one animal, Dog 31, whose records are shown in Fig. 7, was a more distinct negative S-T segment observed. Even here the change was in no way comparable to the changes seen in the cava occlusion after ligation of the coronary artery (c.f. Fig. 7 with Fig. 3).*

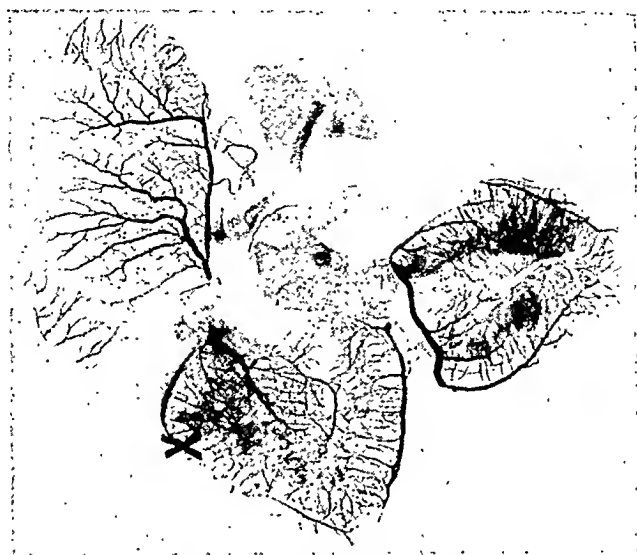


Fig. 8.—X-ray of injected coronary arteries of Dog 16. X indicates location of occlusion of the ramus descendens of the left coronary artery. The three ears in the figure indicate respectively from right to left, the right ventricle, left ventricle, and septum. Note abundance of anastomosis.

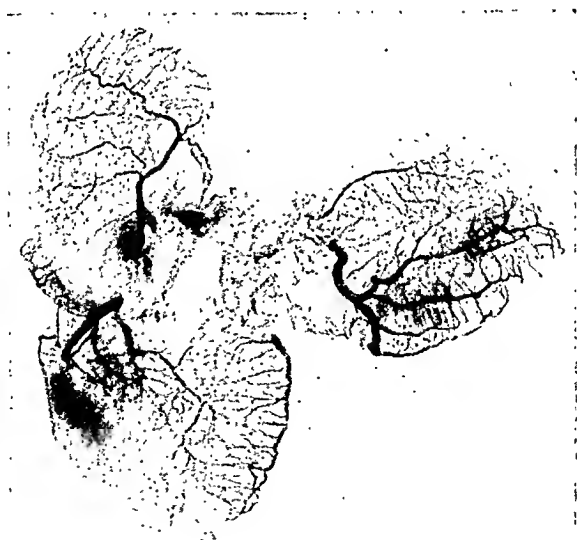


Fig. 9.—X-ray of injected coronary arteries of Dog 30. Showing occlusion of ramus descendens of the left coronary artery. The three ears in the figure as in previous figure. Note almost complete absence of anastomosis.

DISCUSSION

(a) *Relation of the electrocardiographic changes to the level of ligation, to the area supplied by the ligated vessel, and to the abundance of the coronary anastomosis.*

*No change in the S-T interval was observed during slowing following stimulation of the vagus.

In these experiments there is no correlation between the extent of the S-T deviation and the animal's weight, the extent of the area deprived of blood supply, or the level at which the ramus descendens was ligated. Especial attention was paid to the extent of the anastomosis, which was found to vary greatly in different animals, from practically none, as illustrated in Fig. 8, to an abundant one as seen in Fig. 9 (c.f. also Moore¹⁰). Despite this great variation in the abundance of the anastomosis there was no correlation between the anastomosis and the electrocardiographic changes. It may be that this lack of relation is dependent on a variable Thebesian supply, a factor which could not be evaluated.

The lack of R-T deviation associated with normal mechanism in these experiments was not caused by failure of coronary artery ligation. This was shown by the injection of the hearts post-mortem. Every animal showing no changes in the R-T segment after coronary ligation was found on injection to have had complete obstruction of the coronary artery at the site of the tie (e.g. Figs. 8 and 9).

In the face of our negative results from ligation of the coronary artery, we may consider the positive results previously reported. In the first place earlier workers included the vein in the coronary ligation, a factor which must accentuate the ischemia from coronary occlusion alone. In previous experiments, no particular precautions were taken in the use of anesthetics to maintain the systemic blood pressure at a normal level. We found in animals whose left ramus descendens was ligated—with no significant drop in blood pressure—that a lowering of systemic blood pressure from occlusion of the inferior vena cava for five minutes was sufficient to cause R-T deviations to appear. It is apparent, therefore, that unless the systemic blood pressure is maintained at a normal level one cannot conclude that coronary occlusion per se is the sole factor responsible for R-T deviations.

(b) *The Direction of the S-T Deviation.*

Recently Barnes and Whitten¹¹ have emphasized that the direction of the S-T deviation in the various leads may be used in localizing the site of the area infarcted. According to them infarction of the anterior portion of the left ventricle or apex caused a positive S-T in Lead I and a negative S-T in Lead III, and infarction of the posterior wall of the left ventricle produced a negative S-T in Lead I and a positive S-T in Lead III. Our experiments show that while this correlation obtains in the majority of dogs, it is not always present. The area in which the blood supply was interfered with was located, to a variable extent, in the anterior and apical regions of the left ventricle and in the septum. In 18 experiments a change in the level of the S-T interval occurred in Lead I; in 15 of these the S-T was positive and, in 3, negative. This is in fair agreement with Barnes' and Whitten's pre-

diction. But in Leads II and III the disparity is more striking. For example, in the 25 experiments in which a change in the S-T level occurred in Lead II, in twelve the S-T became positive and in thirteen negative. In the twenty-six experiments in which the S-T level changed in Lead III, ten had a positive S-T, and the remainder (16) a negative S-T. However, the most striking shifts of the S-T level were found in those instances in which the S-T in all three leads or at least in Leads II and III became positive. Some of the typical shifts of the S-T intervals are shown in Figs. 2, 3, 4, 5, 6. For example, Fig. 2 (segment 8) has a positive S-T interval in Leads I and II, and a negative S-T in Lead III. Fig. 3 (segment 9) has practically no change in Lead I and a negative S-T in Leads II and III. Fig. 4 (segment 5) has a short negative S-T in Lead I, and a marked positive S-T in Leads II and III. Figs. 5 and 6 show positive S-T intervals in all three leads.

This variability in S-T changes in hearts with the same general area affected indicates the difficulty of localizing the affected region from the direction of the S-T in the electrocardiogram.

(c) *The Rôle of Myocardial Incompetence in Producing the Electrocardiographic Changes Associated with Coronary Occlusion.*

It was stated above that ligation of the ramus descendens of the left coronary artery in the dog caused no characteristic R-T deformities of the electrocardiogram, provided the cardiac mechanism remained normal, whereas a further impairment in blood supply (ligature of the inferior vena cava for five minutes) caused R-T deviations to appear. In the normally beating dog heart there is apparently sufficient collateral circulation to prevent a high degree of local ischemia following coronary ligation. This collateral supply, however, fails to prevent ischemia after ligation of the inferior vena cava.

The hypodynamic state of the heart resulting from an impaired venous return causes (1) a lowering of intraventricular pressure during systole and (2) a sharp fall in systemic blood pressure, factors which reduce the flow through both the Thebesian system and the coronary capillaries. As a result, myocardial ischemia of a degree sufficient to cause R-T deviations in the electrocardiogram appears. It is known that some grade of myocardial incompetence is often associated with or results from coronary thrombosis in man, and our experimental results suggest that the R-T deviations frequently seen in such cases may be due, in part at least, to the hypodynamic state of the heart.

SUMMARY

Ligation of the ramus descendens of the left coronary artery in acute experiments on dogs caused no characteristic R-T deviations of the electrocardiogram provided the cardiac mechanism remained normal. However, a further impairment in the heart's blood supply induced by ligation of the inferior vena cava for five minutes, produced

typical R-T deviations as seen in recent clinical coronary thrombosis, with a return to normal after the venous obstruction was removed.

The appearance of a disturbance in the cardiac mechanism (extrasystoles and tachycardias) following coronary ligation alone produced R-T deviations.

These experiments suggest that R-T deviation is a manifestation of myocardial ischemia in the production of which coronary occlusion is one factor.

REFERENCES

1. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion. I. Clinical, *AM. HEART J.* 5: 68, 1929.
2. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion. II. Experimental, *AM. HEART J.* 5: 77, 1929.
3. Smith, F. M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
4. Hamburger, W. W., Priest, W. S., and Bettman, R. B.: Experimental Coronary Embolism, *Am. J. M. Sc.* 171: 168, 1926.
5. Gold, H., DeGraff, A. C., and Edwards, D. J.: R-T Interval in Experimental Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* 13: 664, 1926.
6. Otto, H. L.: The Effect of Obstruction of Coronary Arteries Upon the T-wave of the Electrocardiogram, *AM. HEART J.* 4: 346, 1929.
7. Clerc, A., Deschamps, P. N., Bascourret, M., and Robert-Lery, J.: Remarques Electrocardiographiques sur la Ligature Des Arteres Coronaires chez le Chien, *Comp. Rend. Soc. Biol.* 103: 223, 1930.
8. Gruber, C. M.: Electrocardiographic Changes in Anoxemia of the Heart, *Proc. Central Soc. for Clin. Research*, 1930, *J. Clin. Invest.* 8: 664, 1930.
9. Gross, L.: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber.
10. Moore, R. A.: The Coronary Arteries of the Dog, *AM. HEART J.* 5: 743, 1930.
11. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.

THE VALUE OF NEEDLE ELECTRODES IN ELECTROCARDIOGRAPHIC DIAGNOSIS*

JOHNSON MCGUIRE, M.D., AND JOHN H. FOULGER, M.D.
CINCINNATI, OHIO

IT NOT infrequently happens that, in taking electrocardiograms with the conventional Einthoven leads, using zinc plate electrodes, the auricular deflections are so obscured (by muscle tremor, low voltage, etc.) that it is impossible to decide upon the true character of auricular activity. This is particularly the case with auricular fibrillation,

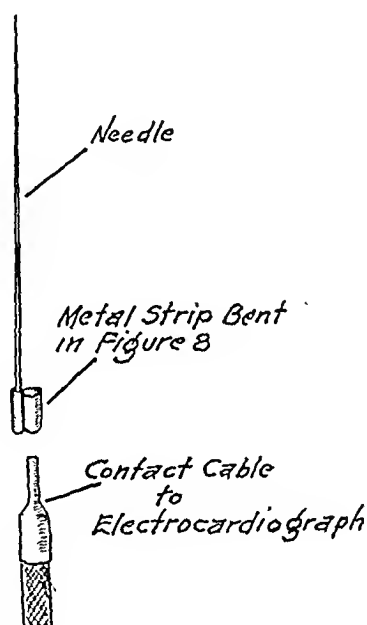


Fig. 1.—Diagram of needle electrodes.

flutter and tachycardia. When such a difficulty occurs, leads from the thorax, with the needle electrodes first suggested by Straub,¹ result in such amplification of the auricular deflections that their true significance can usually be discovered and their rate counted.

Straub found that the site of greatest resistance in the whole system of conduction of heart action currents is the fat-saturated outer layer of the skin. This resistance he could overcome by inserting needles 1 to 2 mm. below the skin surface. Though the needle electrodes were polarizable, he concluded that, since the action current of the heart was small, they would produce no distortion of the electrocardiogram.

*From the Cincinnati General Hospital and the Departments of Medicine and Pharmacology, University of Cincinnati.

Ackermann² compared leads (with needle electrodes) from various points on the thorax with zinc plate leads from the extremities and found that the former showed all the deflections of the normal electrocardiogram with a distinctness often absent from the Einthoven leads.

Wenckebach³ employed thoracic needle leads in the analysis of cases of auricular fibrillation and flutter and concluded that they were of great value.

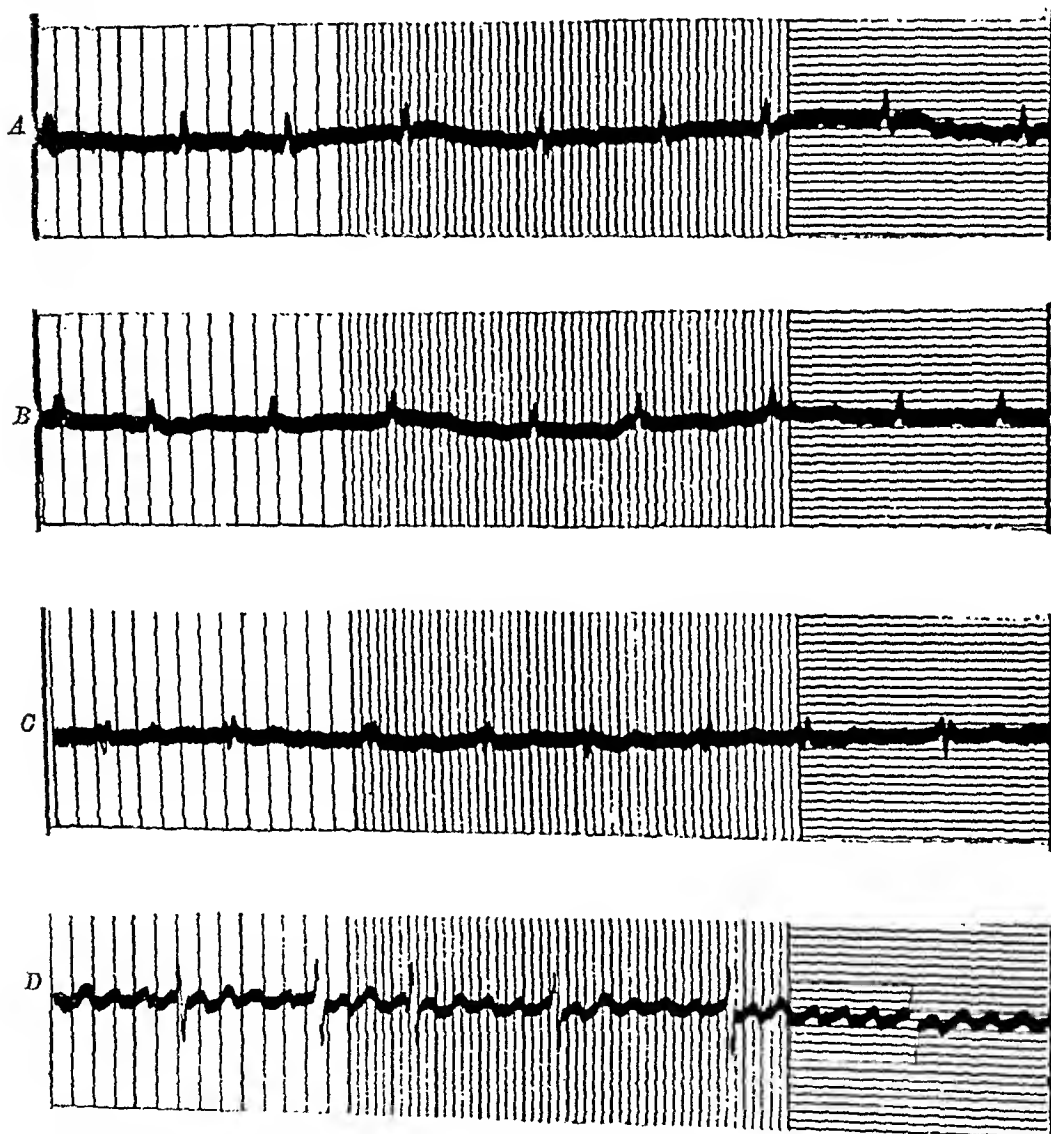


Fig. 2.—Patient 1. A, B, C, the three conventional leads of Einthoven. D, A record taken with needle leads from the chest. The irregular auricular rate, indeterminate from records A, B, C, is seen in record D to be approximately 470 per minute.

Note.—In all figures the standardization was the same for both needle and ordinary leads, viz., 1 millivolt gave a deflection of 1 cm.

This paper deals with three interesting examples in which our doubts as to diagnosis have been clarified by needle lead records.

The Victor electrocardiograph was used in the cases reported here.*

*Unfortunately we were unable to make an extensive study of needle electrodes with string galvanometers. However, using the Hindle instrument in several cases equally good results were obtained.

The needle leads were of simple construction, consisting merely of an ordinary steel sewing needle connected with the tapered metal ends of the cable from the electrocardiograph (after removing the zinc plates) by a strip of metal bent into a figure eight and tightly clamped around both (Fig. 1). After sterilization the needles were inserted at the second and fifth right interspaces at the sternal margin.

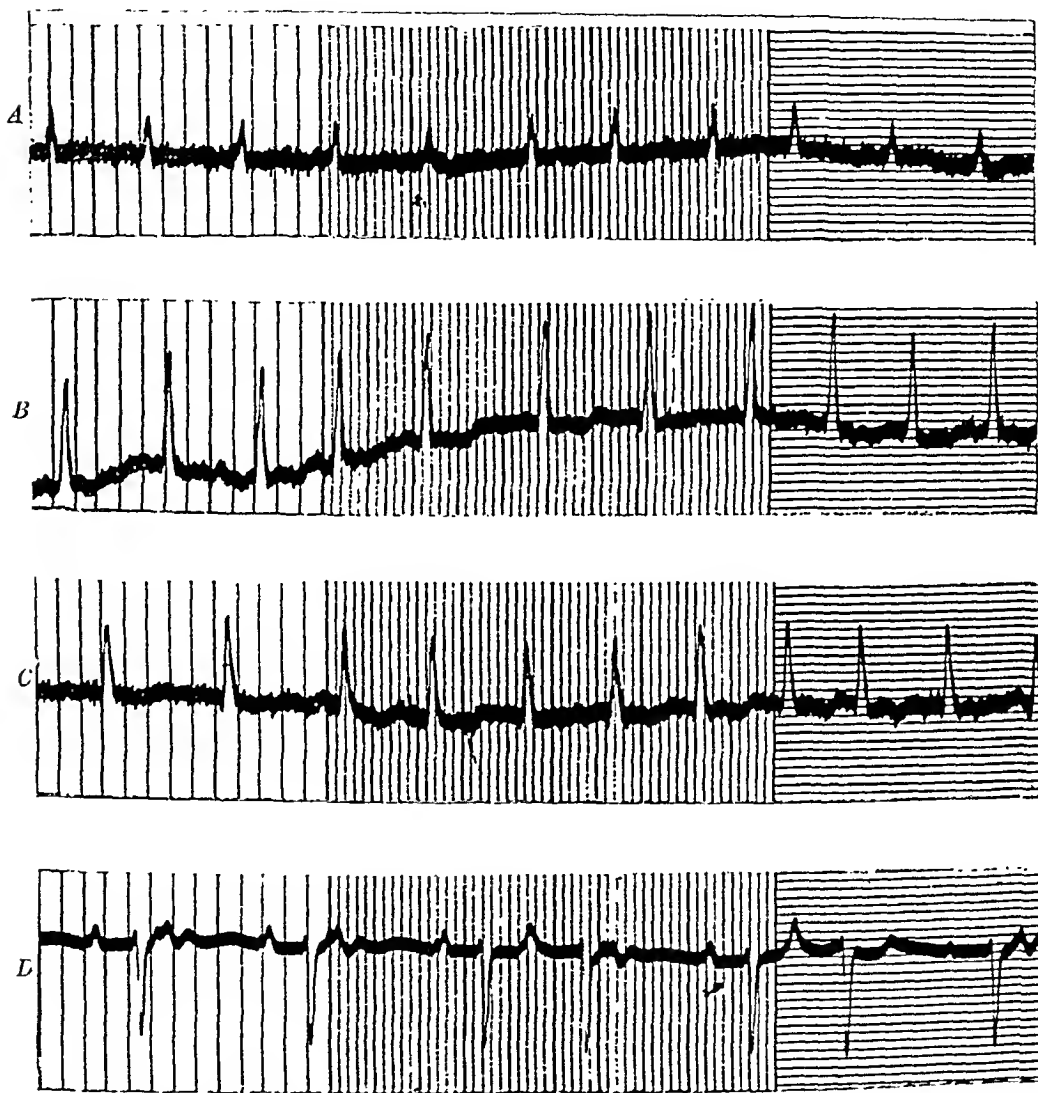


Fig. 3.—Patient 2. A, B, C represent Leads I, II and III. D is a needle lead. The skeletal tremor confusing the record from the extremities is eliminated, and the provisional impression of auricular fibrillation is shown to be erroneous, as the P-waves are clearly inscribed, when not buried in the T-waves. The true diagnosis is partial auriculoventricular block with some auricular premature beats.

It must be noted that, in employing needle leads, one can only make use of those connections with the galvanometer marked to lead from the right arm and the left leg, and that the former must always be connected with the needle inserted in the skin in the second right interspace.

In the following cases the true nature of certain auricular arrhyth-

mias was doubtful, until records were obtained with needle leads. Indeed, in Case 2, diagnosis was made possible only by their use.

CASE REPORTS

CASE 1 (Fig. 2). The patient, a colored male, aged 54 years, was admitted to the Cincinnati General Hospital with the clinical diagnosis of arteriosclerotic heart disease, congestive failure and frequent premature contractions. The electro-

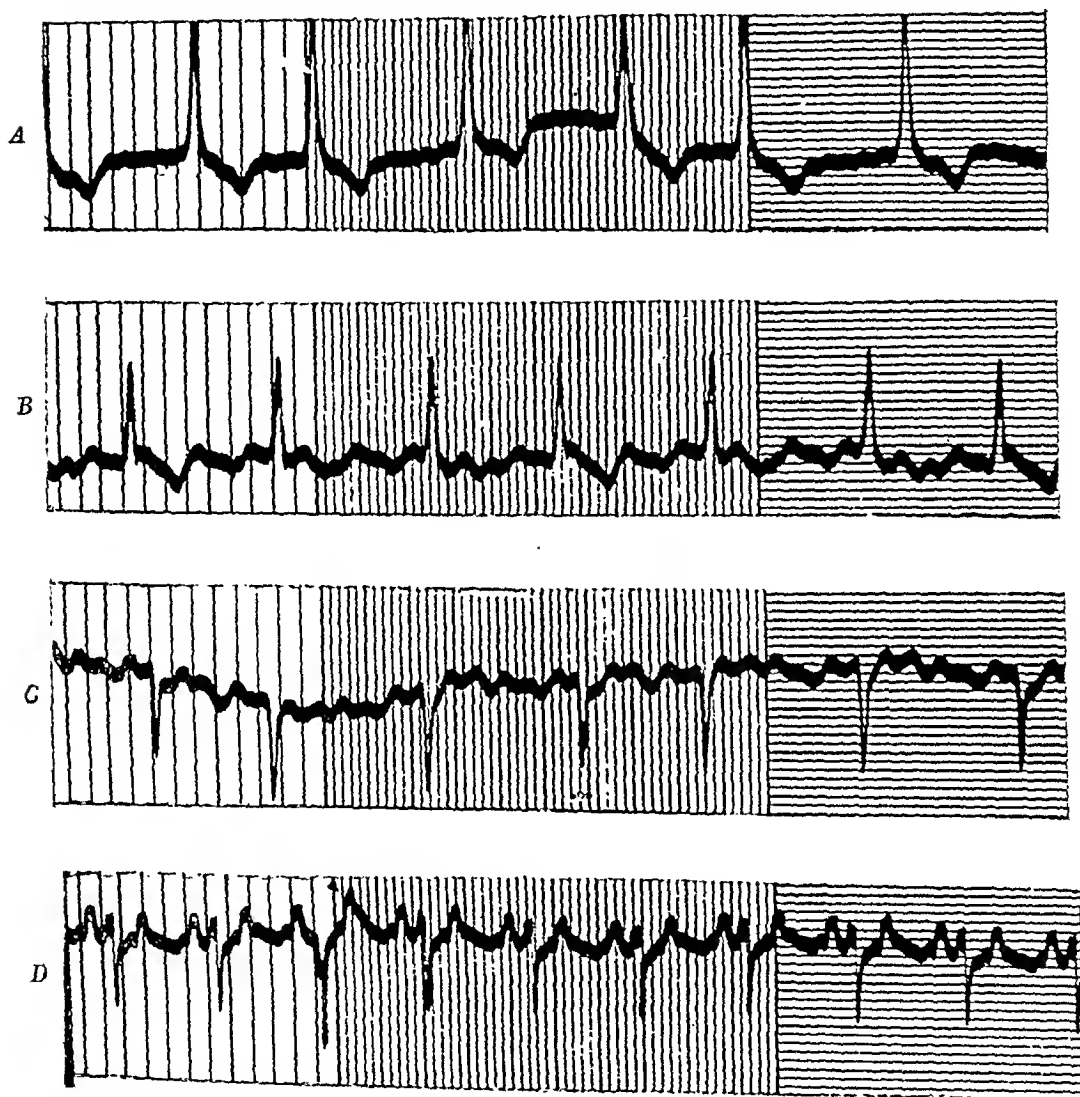


Fig. 4.—Patient 3. Curves A, B, C the standard leads. D is a needle lead. This case, originally thought to be possibly auricular fibrillation, is shown to have a completely regular succession of P-waves with a rate of 250 per minute.

cardiogram, with leads from the extremities, showed a rather irregular rhythm, with low voltage. No "f" waves were discernible. The record suggested auricular fibrillation, but auriculoventricular rhythm (type 2) could not be decisively eliminated. A needle lead record showed definite "f" waves, irregularly spaced, with a rate of approximately 470 per minute.

CASE 2 (Fig. 3). This patient, a white female, aged 65 years, was of special interest, as the clinical picture and the electrocardiogram from the extremities suggested auricular fibrillation. However, the needle lead record (Fig. 2 D), showed clearly that the arrhythmia was due to partial auriculo-ventricular block with auricular premature beats. Complete auriculo-ventricular dissociation was ruled out, for the P-waves were irregularly spaced.

CASE 3 (Fig. 4). The patient, a colored female of 41 years, was admitted with hypertensive heart disease, mild congestive failure and marked cardiac irregularity. A, B and C of Fig. 3 show Leads I, II and III respectively. These records were at first interpreted as due to auricular fibrillation. But careful measurement suggested a regular spacing of the P-waves, especially in Lead III, though many were buried in the ventricular complexes. The needle lead record, Fig. 4 D, showed complete regularity of the auricular waves with a rate of 250 per minute. Consequently, the condition was diagnosed as one of auricular flutter, with varying degrees of block, although the disorder might be paroxysmal auricular tachycardia simulating that of a case reported by White.⁴ Later tracings taken after digitalization (and therefore in the presence of a high degree of block), while showing the same auricular rate, resemble more closely those of auricular flutter. It should be mentioned that before digitalis was given, pressure over the vagi and ocular pressure had no effect upon the heart rate.

CASE 4 (Fig. 5) illustrates the extent to which the P-waves can be amplified by the use of needle electrodes.

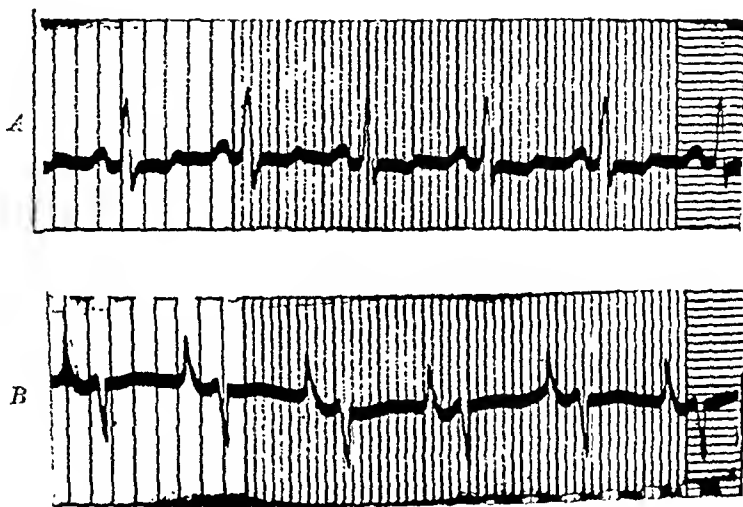


Fig. 5.—Patient 4. A is a section from Lead II with ordinary electrodes. B is a needle lead from the chest. The P-waves are enlarged disproportionately to the ventricular complexes, which are now registered as downward deflections and show the amplification and change in form of the normal P-wave, which usually occurs in needle leads.

SUMMARY

By the use of needle electrodes and thoracic leads, accurate diagnosis can sometimes be made when the interpretation of electrocardiograms made with the ordinary leads is doubtful. Three cases are cited which demonstrate the value of this method. A simple method for the construction of such electrodes is described.

The authors wish to express their appreciation of Dr. Paul D. White's helpful criticisms and suggestions.

REFERENCES

1. Straub, W.: Ueber einen vereinfachten Weg der Ableitung von Elektrokardiogrammen, *Klin. Wchnschr.* 1: 1638, 1922.
2. Ackermann, R.: Ueber thorakale Ableitung des Elektrokardiogrammen, (complete bibliography), *Deutsches Arch. f. klin. Med.* 61: 144, 1924.
3. Wenckebach, K. F., and Winterberg, H.: *Die Unregelmässige Herztätigkeit*, Leipzig, 1927, Wilhelm Engelmann.
4. White, P. D.: Heart Block During Auricular Paroxysmal Tachycardia, *M. Clin. North America* 8: 1855, 1925.

ELECTROCARDIOGRAPHIC STUDIES IN INFECTIOUS DISEASES*

PRELIMINARY REPORT

CHARLES SHOOKHOFF, M.D., AND LEO M. TARAN, M.D.
BROOKLYN, N. Y.

THE heart is involved in the severer types of all the infectious diseases. The bedside symptoms of this involvement, systolic murmurs, indistinct heart sounds, rapid heart rate, generalized weakness, etc., have been recognized by physicians for many years. An arrhythmia has always been considered of great importance in the establishment of such cardiac involvement. Since the introduction of the electrocardiograph into the clinic, gross abnormalities in electrocardiographic curves have been found in the severer types of nearly all the infectious diseases, typhoid fever, influenza, diphtheria, etc. Auricular fibrillation, flutter, paroxysmal tachycardias, nodal rhythm, extrasystoles, sino-auricular block and all the degrees of atrio-ventricular block have been reported.

In rheumatic fever, more than in any of the other infectious diseases, the arrhythmias have played an extremely important part, primarily because of their frequent occurrence. In recent years many observations have been made, not only on the frequency of changes in rate and rhythm, but also on the high incidence of prolongation of the auriculo-ventricular conduction time. (Parkinson, Gosse and Genison, Cohn and Swift,¹ and others.) More recently, Cohn and Swift,² Rothschild, Libman and Sachs,³ and others, have made observations on the frequent occurrence of deviations from normal in the ventricular portion of the electrocardiogram. They described changes in the T-wave and in the R-T or S-T intervals as well as conduction disturbances. Swift⁴ reported such changes in 93 per cent of a series of rheumatic fever patients. All these observers have reported changes in the form of the electrocardiogram from time to time during the course of the disease, changes not always paralleling the clinical signs of severity, i.e., leucocytosis, temperature, joint involvement, etc.

Rothschild, Libman and Sachs³ commented upon the persistence of electrocardiographic findings in a number of their rheumatic fever patients who had been declared clinically well. Shapiro,⁵ in a recent publication, studied electrocardiographic tracings taken on children who gave a definite history of having had rheumatic fever and who

*From the Cardiological Departments of the Jewish Hospital of Brooklyn and the Kingston Avenue Hospital for Contagious Diseases.

were attending school regularly. He found in these children a high percentage of abnormalities occurring particularly in the ventricular portion of the electrocardiogram. In twenty cases of his series he found variations in the form of the electrocardiographic abnormalities from time to time, similar to variations found in active rheumatic fever but to a lesser degree.

The electrocardiographic abnormalities found in rheumatic fever can be thus classified: (1) changes in rate and rhythm; (2) changes in the A-V conduction time, from a slight prolongation of that interval to all the higher degrees of A-V block (3) changes in the ventricular portion of the electrocardiogram involving abnormalities in position and shape of the S-T or R-T interval; height and direction of the T-wave; and height and shape of the main deflection. These changes in themselves cannot be considered specific for any definite disease entity. They have been observed in toxic, degenerative, infections, vascular, metabolic and other types of disease. We believe that electrocardiographic abnormalities, since they are indicative of a disturbed physiology only, cannot in themselves, without clinical data, be used to make a diagnosis of a specific pathological process. Certain diseases seem to have a predilection for the conduction system, however.

Despite our belief in the nonspecificity of electrocardiographic findings, we felt that in rheumatic fever the above described changes might be characteristic for that disease because of: (1) the high incidence of their occurrence; (2) the varying electrocardiographic changes in the course of the disease, changes not always paralleling the clinical signs or severity of involvement; (3) the tendency of these changes to persist; (4) the frequency of conduction disturbances.

Rothschild, Sacks and Libman³ compared electrocardiographic findings in rheumatic fever and subacute infective endocarditis. They found these abnormalities much less frequently in subacute infective endocarditis than in rheumatic fever. No mention, however, was made of the possibility of these findings being due to the previous rheumatic involvement that the patients with subacute bacterial endocarditis might have had.

In order to obtain further light on this question, we decided to make comparative studies in other infectious diseases.

We took electrocardiographic curves during the course of the various infectious diseases and compared these findings with those described in rheumatic fever.

Although considerable work has already been done on normal children, we thought it advisable to control our studies in infectious disease with normal children living in the same environment.

In this preliminary report we present briefly the results of a study of two hundred and fifty-nine normal children between the ages of six and fourteen years; fifty cases of scarlet fever, between the ages of

six and fourteen years and fifty cases of diphtheria in the same age groups, and a comparison of the findings in the latter two diseases with those described in rheumatic fever.

RESULTS

I. *Normal Children*.—On the whole our findings do not, in any great degree, vary from the conclusions drawn by Scham,⁶ Lincoln and Nicolson⁷ and others.

The heart rate decreases as the child grows older, and the female rate is higher than the average male rate. The percentage of cases having a pulse rate above 100 does not strikingly decrease with the increase in age up to nine years; from that age on there is a definite decrease in the percentage occurrence of rates above 100.

Seventy-eight per cent of our normal children have shown a sinus arrhythmia. From the ages of six to nine years there seemed to be a definite decrease in the incidence of sinus arrhythmia with a definite increase in rate; from nine to eleven years, despite a very definite decrease in rate, there was a definite decrease in the incidence of sinus arrhythmia; from the ages of eleven to thirteen years, the incidence of sinus arrhythmia increased very perceptibly, concomitantly with a definite decrease in rate. Extrasystoles were found in only two children—one child had auricular extrasystoles and the other had ventricular extrasystoles. No other arrhythmias were noted.

No abnormalities in the shape of the P-wave were seen in the first or second leads. In 17.6 per cent of this series split, diphasic or inverted P-waves were observed in the third lead.

The average P-R interval in children is much shorter than the accepted maximum normal of 0.20 seconds for adults. Our average for children in the age group studied was about 0.12 seconds, and the range was from 0.08 seconds to 0.16 seconds.

The QRS interval in our series was found to be not more than 0.051 seconds. No abnormalities in the shape of the R-wave or QRS deflections were noted in Leads I or II. In 34.8 per cent of the children there is a slight slurring of the main deflection and a slight widening of the QRS interval seen in the third lead.

We found the R-T or S-T interval isoelectric in the first and second leads in all but four children, and in these four children the distance above or below the line was less than 0.10 mm. No explanation for this possible deviation from the normal could be found in the clinical history.

The average height of the T-wave for the whole series was 3.5 millimeters. No abnormalities of this wave were seen in the first or second leads. Twenty-four and eight-tenths per cent of the children showed an inversion of this wave in the third lead. From the ages of ten to fourteen years there was a very definite decrease in the percentage incidence of inversion of T₃.

The relationship of the length of the P-T to the length of the whole cardiac cycle was studied. It was found that the average P-T interval in these normal children was 71 per cent of the average length of the whole cycle.

In nine children, or 3.4 per cent of our normal series, we noticed an abnormal axis deviation which has persisted for at least two and a half years in four out of five children reexamined within that time.

In twenty-five children studied before and immediately after a given amount of exercise, we found no change in the configuration of the electrocardiographic curve. There were no disturbances in the shape and position of the T-wave or shape and position of the R-T or S-T interval in the first and second leads. No changes in the length of the P-R interval were noted. The only changes noted after exercise were an increase in heart rate and a decrease in the occurrence of sinus arrhythmia.

Daily electrocardiograms were taken on twenty children for two weeks. No changes in the form of the electrocardiogram, either in the T-wave or R-T or S-T interval were noted from day to day in the first and second leads. Changes in the direction of the T-wave in the third lead, however, were observed in three children of this series. Rate changes were frequent. Particular attention was paid to T-wave, R-T and P-R interval changes.

II. *Scarlet Fever*.—There are many relationships that scarlet fever and rheumatic fever seem to have in common. The association of some form of streptococcus to these diseases as a specific etiological factor; the many symptoms of a hypersensitive state caused by some form of this type of organism; the not infrequent activation of a latent rheumatic fever by the occurrence of scarlet fever; the many controversial points in the pathology of these diseases, particularly the conception of Schmorl and Fahr; the many clinical manifestations, tonsillar involvement, joint manifestations, cardiac complications, nephritis, common to both diseases make this comparative electrocardiographic study of interest.

Electrocardiograms were taken during the course of the disease in fifty children suffering from scarlet fever.

We found that the rate did not materially differ in the various age groups from the rate found in normal children. The higher rates, found in the febrile cases, had a definite relationship to the increase in temperature.

The incidence of sinus arrhythmia paralleled the incidence of that arrhythmia in normal children.

A relative bradycardia was observed in 25 per cent of the patients. This marked drop in heart rate was first noted about the tenth day of the disease, and lasted up to about the end of the third or the beginning of the fourth week. No other arrhythmias were noted.

We observed an abnormal axis deviation in 16 per cent of the cases. This deviation, however, returned to normal before discharge from the hospital in all but one child.

No abnormalities in the P-waves were noted. The P-waves, however, were slightly higher in those children having fever than those in the afebrile stage. The average height of this wave in all cases of scarlet fever was 1.9 millivolts as compared with 1.7 millivolts in normal children.

The P-R interval ranged from 0.08 seconds to 0.18 seconds. The average length of this interval was 0.125 seconds. The febrile cases seemed to have a shorter P-R interval. No prolongations of this interval were noted.

No abnormalities or abnormal prolongations of the QRS interval, or of the shape of the main deflection, were noted in the first or second lead.

In 14 per cent of the children minor changes in the position of the R-T or S-T interval were noted in the first or second lead.

Abnormalities in shape and direction of the T-wave in Leads I and II were noted in only 10 per cent of the children. All abnormalities appeared early in the course of the disease and disappeared early in convalescence. No electrocardiographic abnormalities were noted on discharge from the hospital. In 40 per cent of these children an inversion of the T-wave in the third lead was noticed some time during the course of the disease. In 36 per cent T_2 changes only were found. These changes were not considered evidence of myocardial disease although the percentage of inversion of T_2 was higher in scarlet fever than in normal children of the same age groups.

The ratio of P-T to P-P was 70.8 per cent.

Our electrocardiographic findings in scarlet fever differ from those described in rheumatic fever: (1) in the comparative infrequency of abnormalities of the ventricular portion of the electrocardiogram; (2) in the complete clearing up of these abnormalities early in the convalescence; and (3) in the absence of conduction disturbances.

III. *Diphtheria*.—This electrocardiographic study in diphtheria was prompted both by the disturbances found in the ventricular portion of the electrocardiogram in rheumatic fever and also by the endeavor to throw further light on the cause of circulatory failure in that disease.

Fifty consecutive admissions to the diphtheria wards of the Kingston Avenue Hospital for Contagious Diseases were studied. Our series included tonsillar, septic, pharyngeal, laryngeal, and faucial diphtheria. Only mild cases were seen. All children recovered.

In the diphtheria cases the average heart rate was somewhat higher than that found in the scarlet fever or normal children. There was a decidedly higher percentage of cases with rates between 110 and 120 in this disease. This increase in rate was not accounted for by fever.

Fifty-six per cent of the patients showed a sinus arrhythmia. Two cases only showed a relative bradycardia during the second week of the illness. Auricular extrasystoles were noted in only one case.

No abnormalities in either the height or the shape of the P-wave were noted in the first or second leads. P_a changes alone were not considered evidence of myocardial disease.

No prolongation of the auriculo-ventricular conduction time above that considered normal for children was observed. The average P-R interval, however, 0.134 seconds, was slightly higher than that for scarlet fever.

In order to compare the P-R interval in scarlet fever and diphtheria with that in rheumatic fever, the P-R interval in fifty children, between the ages of six and fourteen years, having acute or subacute rheumatic fever was measured. It was found that the mean and standard deviation of the P-R interval in scarlet fever were respectively 0.1256 and 0.0208; in diphtheria 0.1274 and 0.0202; and for rheumatic fever 0.1936 and 0.034. No prolongations of the P-R interval above that considered normal for children were observed.

The average length of the QRS interval in diphtheria was 0.06 seconds. This is somewhat higher than the average for normal children and for children suffering from scarlet fever. In 16 per cent a distinct widening of this period was noted. In these cases a slurring of the descending limb of the R-wave and a high position of the R-T interval was noted. Aberrations in the QRS group in the third lead only were not considered evidence of myocardial disease; they occurred in 40 per cent of the children. This percentage is slightly higher than that found in normal children and in scarlet fever.

Sixty per cent of the children showed disturbances in the shape or position of the R-T or S-T interval. In 16 per cent the R-T interval was a continuation of a slurred descending limb of the R-wave and did not reach the base line; it had its convexity downward and ended as the upstroke of the T-wave. The QRS interval in these children was widened. By far the greatest number of electrocardiographic abnormalities in mild diphtheria were found in disturbances of the R-T or S-T interval. These abnormalities occurred as early as the fourth day of the disease and as late as the fifty-seventh day. In 14 per cent these abnormalities disappeared entirely before discharge from the hospital. In some instances these curves became normal as early as the seventh day and in others not before the sixty-third day of the disease. In 46 per cent of the cases these abnormalities persisted up to the time of discharge from the hospital to some degree. There seemed to be, however, a tendency to improvement.

No relationship was noted between the occurrence of these abnormalities and temperature, heart rate or duration of illness.

Of these children only eleven showed clinical signs of myocardial involvement during the course of the disease.

Abnormalities in the T-wave were noted in eighteen children. Diphasic, iso-electric, depressed or rounded T-waves were considered abnormal. No inversions of this wave in the first or second leads were noted, however. T-wave changes, as well as the R-T interval changes, occurred as early as the fourth day of the disease and as late as the fifty-seventh day.

The ratio between P-T and P-P did not differ to any degree from that of normal children or of children with scarlet fever. It was 71 per cent of the whole heart cycle.

Eighteen per cent of the children showed an abnormal axis deviation; 12 per cent showed a right axis deviation and 6 per cent a left axis deviation. Of the nine children who showed an abnormal axis deviation, seven showed electrocardiographic abnormalities and six showed clinical evidence of myocardial involvement. In only one of these children was the heart found large by roentgen-ray examination.

It seems to us that these electrocardiographic evidences of myocardial disturbances in mild diphtheria without any prolongations of the P-R interval is evidence to support the myocardial theory in circulatory failure in this disease.

We feel that electrocardiographic abnormalities may be the only evidence of myocardial involvement, and that children suffering from diphtheria should not be pronounced free from danger without the benefit of further electrocardiographic studies.

These electrocardiographic abnormalities in diphtheria are similar to those described in rheumatic fever: (1) in that they occur in a high percentage of children who suffer from only very mild diphtheria; (2) that these findings have a tendency to persist; and (3) that electrocardiographic abnormalities may be found when no clinical signs of myocardial involvement are present.

They differ, however, in the absence of A-V conduction disturbances in these milder cases.

REFERENCES

1. Parkinson, Gosse and Gunson: *The Heart and Its Rhythm in Acute Rheumatism*, Quart. J. Med. 13: 363, 1919.
2. Cohn, A. E., and Swift, H. F.: *Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever*, J. Exper. Med. 39: 1, 1924.
3. Rothschild, M. A.: Sacks, B., and Libman, E.: *The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever*, AM. HEART J. 2: 356, 1927.
4. Swift, H. F.: *Rheumatic Fever*, Am. J. M. Sc. 170: 631, 1925.
5. Shapiro, M. J.: *Electrocardiographic Changes in Quiescent Rheumatic Disease in Children and Young Adults*, AM. HEART J. 5: 504, 1930.
6. Seham, M.: *Electrocardiography in Children*, in Abt, I. A.: *Pediatrics*, Philadelphia, 1924, vol. 4, p. 198, W. B. Saunders Company.
7. Lincoln, E. M., and Nicolson, G. H. B.: *The Hearts of Normal Children (III. Electrocardiographic Records)*, Am. J. Dis. Child. 35: 1001, 1928.

INHALATIONAL TREATMENT OF ANGINA PECTORIS AND INTERMITTENT CLAUDICATION*

YANDELL HENDERSON, PH.D.

NEW HAVEN, CONN.

INHALATION of carbon oxide is now administered for various therapeutic and prophylactic purposes. The benefits afforded depend chiefly on the part which carbon dioxide plays in the control of respiration. Resuscitation from asphyxia of the newborn,¹ prevention of postoperative atelectasis and pneumonia,² elimination of ethyl ether,³ of carbon monoxide,⁴ and of other anesthetic and toxic gases⁵ from the lungs and blood, all alike depend upon the increase of pulmonary ventilation under stimulation of the respiratory center by inhalation of carbon dioxide.

INFLUENCE OF CARBON DIOXIDE UPON THE HEART AND BLOOD VESSELS

The equally marked influence of carbon dioxide upon the circulation has not as yet, or to an equal degree, been exploited for therapeutic purposes. Yet, simultaneously with the modern development of respiration, physiology has produced also observations indicating a powerful influence of carbon dioxide upon the heart. In a long series of experiments,⁶ from fifteen to twenty-five years ago, my collaborators and I demonstrated on dogs, under artificial respiration or breathing naturally under a slight pressure of air after the opening of the thorax, a condition verging on tetanus of the heart—in the physiological sense of the word tetanus, that is a fusion of successive beats. This state was effectively counteracted and heartbeats of full amplitude were restored as a consequence of the restoration of a normal, or perhaps slightly excessive, carbon dioxide content in the blood. The lesson of these observations is now generally applied in experiments upon the isolated heart in the Starling⁷ heart-lung preparation. It is recognized that the blood for perfusion, in addition to being oxygenated, must also be supplied with a sufficient amount of carbon dioxide to overcome the tendency of an exposed or excised heart to develop an inadequate diastolic relaxation. Otherwise it passes into a continuous systolic state, an incomplete tetanus or cramp of the heart.

Following these observations upon the heart, it was shown in another series of experiments⁸ that carbon dioxide may exert an equally strong influence upon the peripheral circulation, and particularly upon the volume of the venous return to the right heart. Clinically this

*From the Laboratory of Applied Physiology, Sheffield Scientific School, Yale University.

effect is best seen as a result of the inhalation of carbon dioxide after a prolonged and extensive surgical operation under open ether anesthesia. The return of blood to the cutaneous vessels, the flushing of the skin, the refilling of the veins previously collapsed, bear at least a superficial similarity to the effects induced by inhalation of amyl nitrite. But the effects, like those of a hot bath and in contrast to amyl nitrite, are more physiological than pharmacological; they are lasting and are accompanied by a restoration of a full strong heart action and a recovery of normal arterial pressure. Never in my experience have there been any symptoms suggesting an overloading of the heart.

Among the various treatments of heart disease, that at Nauheim is the most celebrated. It consists in baths in carbonated water. The good effects, which the treatment is claimed to have, have never really been explained. There is a stimulating action upon the skin, but there is little ground for believing that a slight cutaneous hyperemia can by itself be of much benefit. It is at least possible that the greater part of the benefit sometimes derived from the Nauheim treatment is due rather to inhalation of the carbon dioxide volatilizing from the surface of the bath.

DECREASE OF ANGINA UNDER INHALATION

With these considerations as a physiological background, it has seemed to me justifiable to try, with all due caution at first, the influence of carbon dioxide inhalation upon cases of angina pectoris which are as yet in their earlier stages, but in which moderately severe suffering on exertion is already developing. This is not an emergency treatment, but a therapy for prolonged application. The inhalations are not given during an attack of pain, but at regular times every day, usually before the midday and evening meals, and at bedtime. The patient lies quietly on his back for a few minutes holding over his own face a mask which has a sufficiently large opening to the outside air to offer no resistance to breathing. He is told to keep his mouth open and to breathe deeply rather than rapidly. Then a stream of carbon dioxide gas through a small rubber tube from a cylinder of the pure liquefied substance is fed to the mask. At first the flow is kept small, but as respiration gradually deepens the amount of the gas is increased until at the end of two or three minutes a maximal or nearly maximal depth of breathing is developed. The stimulation is not, however, pushed to the point of increase of rate. This condition is maintained for fifteen or twenty minutes continuously. Then the gas is shut off, and the patient is directed to lie quiet for ten minutes more, so as to avoid the slight giddiness which occurs if he gets up immediately.

It is to be noted that the technic of this inhalation differs markedly from the use of a mixture of oxygen and 7 per cent carbon dioxide, which is best employed for resuscitation from asphyxia. The inhalation used on these heart cases is on the contrary essentially like that applied by Henderson, Haggard and Coburn, and by White after anesthesia and operation.³ A mixture of oxygen and carbon dioxide is rather expensive, and a cylinder of it is exhausted in a single inhalation; while on the contrary even a small cylinder of liquid carbon dioxide lasts for several weeks of this treatment, so that its cost, aside from the control apparatus, is slight. *But of course pure carbon dioxide should be used only with such an open mask that the small volume of the gas supplied is diluted by the patient's breathing in the relatively large volume of the inspired air.*

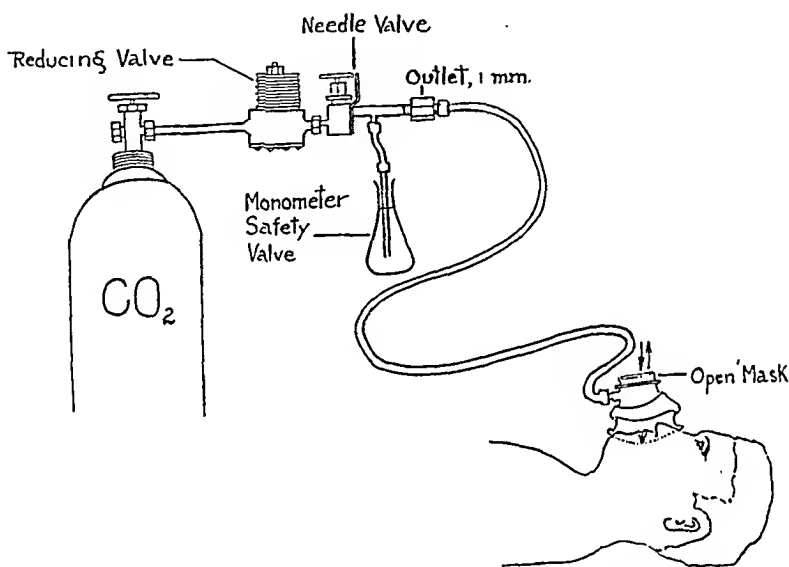


Fig. 1.—Apparatus for administration of inhalation of carbon dioxide with the inspired air. For description and use, see text.

The essentials of the control apparatus employed are (a) an open mask, as above described, and (b) a device for the control of the flow of the gas to the mask, so that by no possibility can the patient receive an excess; it must be fool proof.

For this purpose a water manometer only 100 to 120 mm. long is so arranged that it not only serves as a gauge but also as a safety valve, through which any excess supply of the gas blows off into the air without going to the mask. It is merely a straight glass tube, 5 mm. bore, which extends down for this distance below the surface of water in a bottle, flask or test tube. Between this manometer and the tube leading to the mask is a hole of not more than 1 mm. diameter. Thus the maximum volume of gas that can go to the mask is that which under a pressure of 100 to 120 mm. of water column will pass through a 1 mm. hole. The supply of gas to the manometer and to this milli-

meter hole is controlled either by a finely adjustable needle valve, or better by a McCaa reducing valve and a needle valve, as shown in Fig. 1.* If only the needle valve is used, it has to be frequently re-adjusted by the person administering the inhalation. If the reducing valve is used also, the flow is so steady that an intelligent patient may manage the entire procedure for himself. This is a distinct advantage in a treatment which the patient may find it necessary to continue one or more times a day for the remainder of his life. For the utmost that can be expected, or even hoped, in regard to such a disorder as angina pectoris is not absolute cure, but a check upon the fundamental conditions, prevention of suffering and prolongation of life.

The effects of this inhalation on the patients thus far treated, as yet only three in number and none with high arterial pressure, have been, in addition to the deeper respiration, as follows: There is a distinct improvement in the color and temperature of the lips and skin, previously rather bloodless or bluish and cold, but becoming warm and pink under the influence of carbon dioxide upon the peripheral circulation. Arterial pressure and the pulse rate are not in appreciable degree increased, although a markedly fuller circulation is evident. The sensation of oppression in the chest, and the pain or "pins and needles" in the shoulder and arm is considerably decreased, and may cease altogether for some hours after the inhalation. After some weeks of daily inhalations the capacity to take such exercise as walking uphill is markedly increased, and the chief difficulty is to prevent the patient from overexerting his partially restored physical capacity.

This is all that it seems justifiable to report in an initial communication on a treatment which will certainly need far more evidence before it can be regarded as of proved general therapeutic value. The cases thus far treated have, however, appeared so much benefited and the technic here described appears to be so safe, that it seems best to put the matter on record, in order that others also may try it for a class of patients for whom there is otherwise little that can be done to relieve or even to delay the development of a peculiarly painful, anxious and hopeless form of invalidism, with an ever-present risk of sudden death from coronary thrombosis.

Mention may also be made here of the effects of this inhalation upon two cases of intermittent claudication in the lower extremities. In both of these cases a marked improvement in the circulation of the ischemic limb was observed under the inhalation, and in one in which the treatment was continued for some weeks there was a distinct cumulative beneficial effect. These cases were studied particularly in the belief that if the pain in angina pectoris and that in intermittent

*An apparatus of this type without the McCaa reducing valve may be obtained from the Foregger Company, 47 West 42nd Street, New York City. An apparatus with the reducing valve from the Mine Safety Appliances Company, Pittsburgh, Pa.

claudication are due to similar local reactions, improvement in both types of cases would tend to support the probability that in both the results are real and not imaginary, either in the patient or in the mind of him who has applied the treatment.

THEORETICAL CONSIDERATIONS

The general conception under which these observations were made was as follows: In a normal person muscular exertion induces no pain either in a limb or in the heart, for the reason that the blood supply is sufficient to afford all the oxygen needed initially in the working parts. This supply of oxygen quickly converts a large part of the fatigue products, especially lactic acid, into carbon dioxide. The carbon dioxide then induces a relaxation of the blood vessels and thus increases the blood supply to the working parts, both heart and limbs. This is the normal reaction to exercise. The healthy man takes a walk or plays an athletic game to improve the oxygenation of his tissues. Thus as Miescher⁹ said forty-five years ago: "Carbon dioxide spreads its protecting wings over the oxygen supply of the body."

Quite different is the reaction in a person in whose heart or limbs the blood vessels are sclerotic or constantly contracted. The blood supply and therefore the oxygen supply are insufficient for the initial requirements of exertion. Lactic acid and other fatigue products accumulate; for in the absence of a large supply of oxygen they cannot be burned to carbon dioxide. They tend to induce a cramp of the musculature, cardiac or striated, in contrast to the influence of carbon dioxide which, as I long ago demonstrated experimentally on the heart, promotes relaxation.⁶ To do effective work a muscle must be able to relax as well as to contract. From excess of lactic acid and local deficiency of carbon dioxide come the abnormal reaction to exercise, the ischemia and the cramp.

If now a patient who is liable to such an abnormal reaction receives an inhalation of carbon dioxide, still a third form of reaction develops. He experiences the benefits, without the disadvantages, of physical exercise. He makes no exertion. His muscles are at rest, and his heart is put under no additional strain. There is no decrease of the oxygen supply to any part, but rather an increase, for the carbon dioxide inhaled induces a relaxation of the finer blood vessels, a more ample heartbeat, and a fuller circulation. The balance of supply and demand for oxygen in the tissues is thus distinctly improved and the tendency to cramp is diminished. Furthermore as the treatment is repeated day after day the blood vessels and the heart muscle, under the influence of an essentially normal physiological agent and an essentially normal reaction, gradually acquire and retain a state of decreased habitual strain and more normal behavior. Along these lines

we may figure to ourselves why and how inhalations of carbon dioxide may exert a beneficial effect both immediate and to some degree lasting.

In support of this general conception mention may here be made also of the extraordinary observations which were reported by the late Dr. A. S. Loevenhart¹⁰ in which he found that inhalation of carbon dioxide administered to cases of catatonia caused a temporary restoration of mental responsiveness. The simplest explanation of the results in these cases is to postulate an habitual contraction of blood vessels in the brain of the catatonic patient and to assume that the influence of carbon dioxide upon these vessels is similar to that upon the peripheral circulation elsewhere in the body. The effects of over-breathing in inducing, and of oxygen and carbon dioxide in temporarily inhibiting, fits in epileptics¹¹ are also suggestive of a similar conception.

Finally I have pleasure in acknowledging my indebtedness to my colleague, Dr. George Blumer, for the opportunity to work on one of the cases here reported, and to Dr. Samuel C. Harvey for two of the others. Investigations on the experimental side of this general problem are now being published from Dr. Harvey's laboratory, and further investigations upon patients are to be conducted in the clinic here.

CONCLUSION

Daily inhalations of carbon dioxide appear to offer a possibility of considerable amelioration of the crippling effects and suffering in cases of angina pectoris and also of intermittent claudication.

REFERENCES

1. Henderson, Y.: The Prevention and Treatment of Asphyxia in the New-Born, *J. A. M. A.* 90: 583, 1928.
Incomplete Dilatation of the Lungs as a Factor in Neonatal Mortality, *J. A. M. A.* 96: 495, 1931.
2. Henderson, Y.: Acapnia as a Factor in Postoperative Shock, Atelectasis and Pneumonia, *J. A. M. A.* 95: 572, 1930.
3. Henderson, Y., Haggard, H. W., and Coburn, R. C.: The Therapeutic Use of Carbon Dioxide After Anesthesia and Operation, *J. A. M. A.* 74: 783, 1920.
White, J. C.: Deëtherization by Means of Carbon Dioxide Inhalations, *Arch. Surg.* 7: 347, 1923.
4. Henderson, Y.: The Dangers of Carbon Monoxide Poisoning and Measures to Lessen These Dangers, *J. A. M. A.* 94: 179, 1930.
5. Henderson, Y., and Haggard, H. W.: Noxious Gases and the Principles of Respiration Influencing Their Action. American Chemical Society Monograph Series, New York City, 1927, The Chemical Catalog Company.
6. Henderson, Y.: Acapnia and Shock. I. Carbon Dioxide as a Factor in the Regulation of the Heart Rate, *Am. J. Physiol.* 21: 126, 1908.
7. Starling, E. H.: Linares Lecture on the Heart, London, 1918. Also Knowlton, F. P., and Starling, E. H.: The Influence of Variations in Temperature and Blood Pressure on the Performance of the Isolated Mammalian Heart, *J. Physiol.* 44: 206, 1912. Also Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricles, *J. Physiol.* 48: 357, 1914; with Piper, H.: The Regulation of the Heartbeat, *J. Physiol.* 48: 465, 1914.

8. Henderson, Y., and Harvey, S. C.: VIII. The Venopressor Mechanism, *Am. J. Physiol.* 46: 553, 1918.
Bryant, J., and Henderson, Y.: Closed Ether and a Color Sign, *J. A. M. A.* 65: 1, 1915.
9. Miescher, F.: Bemerkungen zur Lehre von den Athembewegungen, *Archiv. f. Anat. u. Physiol.* 1885. *Physiol. Abtheilung*, p. 355. Republished in *Die Histochemischen u. physiologischen. Arbeiten von Friedrich Miescher.* Verlag F. C. W. Vogel, Leipzig, 1897.
10. Loevenhart, A. S., Lorenz, W. F., and Walter, R. M.: Cerebral Stimulation, *J. A. M. A.* 92: 880, 1929.
11. Lennox, W. G., and Cobb, S.: Epilepsy, *Medicine* 7: 162, 1928.

Department of Clinical Reports

A CASE OF PATENT DUCTUS ARTERIOSUS WITH PRIMARY BACTERIAL PULMONARY ENDARTERITIS*

W. H. TRIMBLE AND RALPH M. LARSEN
NASHVILLE, TENN.

CLINICAL OBSERVATIONS

A 15 year old white girl entered the Vanderbilt University Hospital October 4, 1929. She complained of cough, weakness, and loss of weight of ten weeks' duration. In July, 1929, she suddenly experienced severe pain in the lower part of the left chest, which was increased by respiratory movements and later was associated with chills, night sweats, fever, cough and blood tinged sputum. She was in bed five weeks with this illness, during which she lost twenty pounds. At the end of this time there was a short remission after which she was forced to return to bed where she remained until her admission to the hospital in October.

The past history revealed that she had been a normal healthy child who was capable of the normal exertions of other children of her age. At no time had she been cyanotic, dyspneic, or edematous. She had not had rheumatic fever or chorea.

The physical examination on admission revealed striking emaciation, pallor and generalized muscular weakness. Her temperature was 102° F. and pulse rate 120 without much increase in respirations. The heart was beating forcibly as well as rapidly. The rhythm was regular. The cardiac measurements were as follows: left border 10 cm. from the midsternal line in fifth interspace, right border 3.3 cm. in the fourth interspace. There was also a demonstrable increase in the cardiac dullness in the left first and second interspaces measuring 5.3 cm. to the left of the midsternal line. In the pulmonic area there was a blowing continuous murmur with accentuation of the systolic phase associated with a faintly palpable thrill. The pulmonic second sound was loud and the shock could be palpated. The percussion note was impaired, and there was a moderate number of moist râles over the left lower lung. The spleen was not palpable at this time. She had no petechiae, edema, clubbing or cyanosis.

The laboratory findings showed red blood cells 2,710,000, hemoglobin 50 per cent, white blood cells 15,780. Differential: 79 per cent neutrophils, 16 per cent small lymphocytes, 0.5 per cent eosinophiles, 5.5 per cent large monocytes, 1 per cent unclassified. Urinalysis showed a persistent albuminuria without red blood cells. Blood cultures revealed streptococcus viridans on many different occasions.

On the basis of these findings the diagnosis of patent ductus arteriosus with a superimposed nonhemolytic streptococcal endarteritis of the pulmonary artery near the orifice of the duct was made. This diagnosis was made on the evidence, both clinical and bacteriological, of subacute bacterial endocarditis plus the signs of a congenital cardiac anomaly, namely a patent ductus arteriosus. The lung signs were interpreted as due to pulmonary infarcts. It was thought that the vegetations were on the pulmonary side of the ductus on account of the absence of petechiae and hematuria, and because of the pulmonary infarcts. Also there were no murmurs to suggest that the mitral valve was diseased at this time.

*From the Departments of Medicine and Pathology, Vanderbilt University School of Medicine.

Her course, as one would expect, was progressive, but she lived for six and a half months after her first admission or eight and a half months after the onset of her illness. During the last six and a half months of her life she was admitted to this hospital three different times. During these periods she received a total of thirteen blood transfusions which brought about a transient relief from the symptoms of anemia.

During the first admission she improved definitely. Although she gained eight pounds and was able to be up part of the time, the fever and tachycardia continued. The results of the second and third admissions were not so gratifying. Each time she was more anemic and responded less to transfusions. Blood cultures always contained streptococcus viridans. Late in the illness she began to show petechiae and hematuria, and the spleen became palpable.



Fig. 1.—The anterior flap of the right ventricle has been turned back so that the pulmonary artery is exposed in the upper left hand portion of the photograph. Attached to the orifice of the ductus arteriosus approximately one centimeter above the normal thin pulmonary valves, is the huge vegetating thrombus which almost occludes the pulmonary artery. The extensive overgrowth of this thrombus by endothelium is obvious from the photograph. The depression immediately below the thrombus represents the aneurysm described at autopsy. In the lower portion of the ventricular cavity the normal tricuspid valve is visible. The ventricular hypertrophy and dilatation are obvious.

She was not frequently observed during the last month of her life and died at her home on April 17, 1930. During the last few days she developed anasarca, profound anemia, and coma.

Notes of the post-mortem examination, which was restricted to the chest and the removal of the heart, are as follows:

"The lungs are riddled with nodular, reddish, discolored areas, some of which are fluctuant. A portion of the left lower lobe anterolaterally is widely adherent to the chest wall by dense fibrous marginal adhesions and the underlying lung is fibrotic.

"The heart weighs 290 gm. Both left and right ventricles are enlarged. The pulmonie valve is entirely normal. The pulmonary arteries beyond the main bifurcation are smaller than normal, measuring approximately 0.75 cm. in diameter. The

ductus arteriosus is widely patent and cylindrical, measuring 1.5 cm. in length and 0.5 cm. in diameter. The aortic opening is easily probed but the pulmonary opening is closed by a large greenish-gray, friable, firmly adherent vegetation lying in the pulmonary artery and invading the pulmonic orifice of the ductus. This mass of vegetation measures 2.5x1.5x1.5 cm. and almost completely occludes the pulmonary artery at its bifurcation. A small aneurysmal dilatation of the pulmonary artery 1 cm. in diameter is present about 0.5 cm. heartward from the vegetation.

"The mitral valve measures 7 cm. Scattered along its free edge are numerous grayish-red, friable, loosely but definitely adherent vegetations. On its septal cusp there is present a large vegetative mass 0.5x1.0x0.75 cm.

"The aortic valve is entirely normal. There is no stricture of the aorta or of its isthmus. The left ventricular myocardium measures 1.25 cm. at the apex and 1.75 cm. at the base. The cavity is one and a half times its normal size. The right ventricular wall measures 0.75 cm. at its apex and 1.25 cm. at the base. Its cavity is enlarged to twice its normal size.



Fig. 2.—A "close up" photograph of the pulmonary artery and the ductus. Here again the huge vegetation is seen in the upper left hand portion of the photograph. Immediately to its right the patent ductus, its lumen plugged by a portion of this thrombus, is visible. The apparent puckering of the intima of the ductus is a fixation phenomenon.

"*Microscopic Notes:* The superficial vessels of the epicardium are markedly congested and the tissues widely hemorrhagic. Extensive infiltration by polymorphonuclear leucocytes along the trabeculae is evident. The myocardium of both ventricles is edematous. The muscle cells are large with hypertrophic nuclei, and of these some are fragmented. Focal microscopic areas occur throughout the substance of both ventricles in which the coronary arterial branches are thrombosed by hyalinized emboli. In two of these thrombi coccoid bacteria are demonstrable. The surrounding muscle cells are hyalinized, eosinophilic, and together with adjacent interstitial tissue, markedly edematous, and infiltrated with polymorphonuclear leucocytes. The muscle cells at the periphery of these necrotic areas are swollen by myriads of fat vacuoles.

"The pulmonic vegetation consists of a central core of fibrous tissue from the periphery of which the thrombus is undergoing rapid organization. The vegetation

covering the central fibrous core consists of laminated fibrin bands heavily infiltrated with polymorphonuclear leucocytes and bordered by a massive zone of bacteria which extends in huge colonies into the depth of the thrombus. The bacteria are gram-positive streptococci.

Anatomical diagnoses: (1) Subacute bacterial endocarditis, viridans, affecting the pulmonary artery (ductus orifice) and mitral valve; (2) Congenital cardiac anomaly, patent ductus arteriosus; (3) Stricture of terminal pulmonary arteries; (4) Pyemia, subacute bacterial endocarditis (viridans); (5) Pulmonary infarcts, septic; (6) Myocarditis, focal, acute, septic emboli; (7) Cardiac hypertrophy and dilatation, biventricular."

DISCUSSION

Pateney of the ductus arteriosus is not at all rare, but there are extremely few cases in which the duct seems to be the original seat of

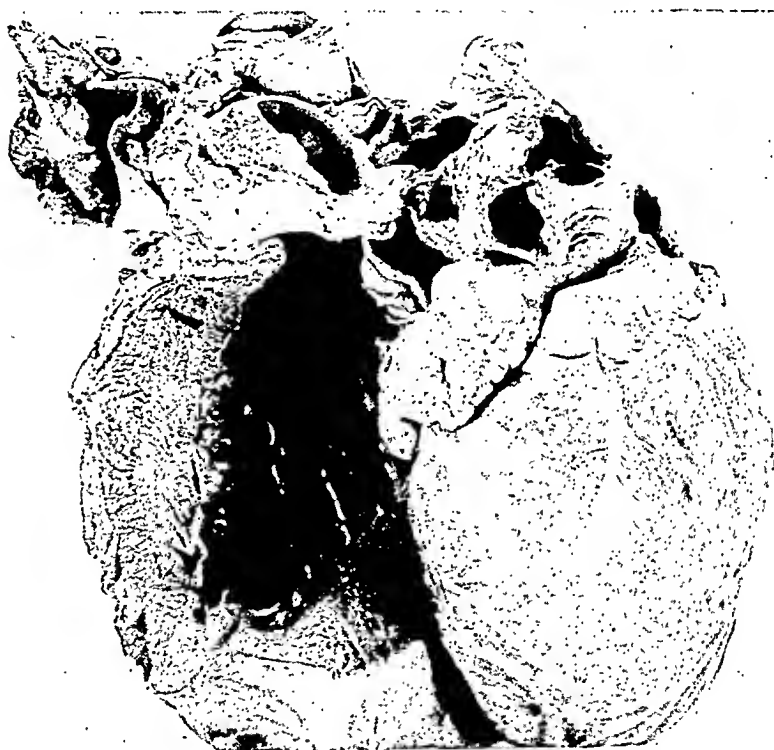


Fig. 3.—The gross photograph of the left side of the heart. The pulmonary artery and patent ductus are visible in the upper left hand field of the photograph. The rather marked hypertrophy of the left ventricular wall is obvious in this photograph.

a vegetative endarteritis. Hamilton and Abbott¹ in 1914 reported such a case in a girl of 19 years. In their case the vegetations were located around the pulmonary orifice of the duct. There were numerous embolic abscesses in both lungs, and pneumococci were found in blood culture, in the vegetations and in the embolic abscesses. Coarctation of the aorta was also present. Schlaepfer² in 1926 reported a case in a boy, aged 8 years, in which there was an organizing and acute arteritis of the pulmonary artery and ductus arteriosus with thrombotic occlusion of both the duct and the pulmonary bulb. There were multiple pulmonary and splenic infarcts, and the streptococcus

viridans was found in blood culture. Krzyszkowski³ in 1902 reported a case in a female, aged 17 years, in which a vegetation was found on the wall of the pulmonary artery just above the pulmonary valves. There was an aneurysmal dilatation of the pulmonary artery opposite the orifice of the ductus arteriosus, and pulmonary infarcts were present. A bacteriological diagnosis in Krzyszkowski's case was not made. The literature of pulmonary endarteritis has been reviewed by Hamilton and Abbott¹ and by Schlaepfer.² In all there are nineteen cases of pulmonary endarteritis, but of these sixteen showed one or more valvular lesions in association with the pulmonary endarteritis.

This case is one in which, although the pulmonary endarteritis is not the only cardiac lesion, the pulmonary artery can be shown to be the



Fig. 4.—A view of the left ventricular cavity. Extensive recent friable thrombi are adherent along the auricular surface of the mitral valve. The closed foramen ovale is visible above.

primary seat of disease. This is demonstrated by the absence of mitral murmurs at the time the patient had conclusive evidence of right sided bacterial endocarditis, the absence of peripheral embolic phenomena until late in the illness and the presence from the beginning of signs which were interpreted as pulmonary infarcts. In addition the pathological study indicates that the pulmonary endarteritis was an older and more advanced lesion than the mitral lesion.

The findings which led to the diagnosis of the pulmonary endarteritis were: a continuous blowing murmur in the pulmonic area with accentuation of the systolic phase; a loud pulmonic second sound and a faint thrill in the same area; an extension of the cardiac outline to the left in the first and second interspaces which was shown both by

percussion and x-ray examination; pulmonary infarets without peripheral emboli and the occurrence of *Streptococcus viridans* in blood cultures.

SUMMARY

A case of pulmonary endarteritis, with the vegetation superimposed upon the wall at the orifice of a patent ductus arteriosus, which was diagnosed clinically six and a half months before death and confirmed by autopsy, is reported. Although the mitral valve was also the site of vegetations, the pulmonary endarteritis is shown to be the primary lesion.

REFERENCES

1. Hamilton, W. F., and Abbott, Maude E.: Patent Ductus Arteriosus with Acute Infective Pulmonary Endocarditis, *Tr. A. Am. Phys.* 29: 294, 1914.
2. Schlaepfer, Karl: Chronic and Acute Arteritis of the Pulmonary Artery and of the Patent Ductus Arteriosus, *Arch. Int. Med.* 37: 473, 1926.
3. Krzyszkowski, J.: Aneurysma des Stammes der Pulmonalarterie und multiple Aneurysmen ihrer Verastelungen bei Persistenz des Ductus Botalli, *Wien. klin. Wchnschr.* 4: 92, 1902.

PERICARDIAL EFFUSION OF UNKNOWN ETIOLOGY NECESSITATING REPEATED PARACENTESIS*

R. H. McDONALD, M.D.
CLEVELAND, OHIO

CASE REPORT

The patient was a boy nine years of age, born of Italian parentage in the United States. On October 19, 1927, he was brought to the Clinic by his parents, who stated that during the preceding month he had complained of occasional colicky pain in the stomach unaccompanied by nausea or vomiting. The bowel movements had been perfectly regular. He also complained that during the preceding two weeks he had been short of breath on exertion, and during this period his mother had noted coldness of the extremities and a bluish discoloration of the lips and ears. His appetite had been poor during the preceding month, and he had lost some weight.

The patient's past illnesses included measles and occasional colds and sore throats. Tonsillectomy and adenoidectomy were performed in 1923. In the spring of 1927 the patient had two attacks of bronchitis, and in the opinion of his parents he had not regained his normal health since that time.

Examination.—The patient was a moderately well-developed and well-nourished boy four feet in height and weighing 53 pounds. The ears and the mucosa of the lips showed a marked cyanotic tint, and there was a mottled cyanotic discoloration of the skin of the chest, abdomen and lower extremities. The boy did not appear to be in distress and there was no increase in the respiratory rate. His temperature was 98°, pulse rate 108, and blood pressure 90/64 mm.

Examination of the chest revealed marked bulging on the left side rendering it asymmetrical. Respiratory movements were practically absent on this side, and there was dullness on percussion over the entire left chest anteriorly, with the exception of the region superior to the second costal cartilage, especially in the axillary area. Posteriorly there was marked diminution of resonance over the lower two-thirds of the left lung. Breath sounds were indistinct over the entire left lung and over the base of the right lung. No adventitious sounds were heard. The external limit of cardiac dullness in the left fifth interspace was 10.5 cm. from the midline and 5.5 cm. in the right fourth interspace. The heart sounds were regular and rhythmical but very indistinct. There was a well-marked pulsus paradoxus. The edge of the liver was palpable two inches below the costal margin in the right midclavicular line. A small amount of free fluid was observed in the peritoneal cavity. There was no demonstrable enlargement of the spleen.

A diagnosis of pericardial effusion was made, and in view of the evidence of pressure, aspiration was carried out through the left fourth interspace, one inch beyond the sternal margin. Approximately 1000 c.c. of a clear, slightly amber fluid were removed without difficulty. By the time the aspiration was complete, the cyanosis was gone, the liver edge was just palpable under the costal margin, and the patient announced himself feeling well and hungry. He was put to bed, and given large doses of salicylates. Three weeks later the effusion recurred, and again 1000 c.c. of fluid were removed. Subsequently, over a period of one year, quantities of fluid varying from 500 to 1800 c.c. were aspirated at intervals of

*From the Cleveland Clinic.



Fig. 1.



Fig. 2.



Fig. 3.

Fig. 1.—Roentgenogram showing a case of marked pericardial effusion which obliterated the heart shadow.

Fig. 2.—Roentgenogram of chest, showing pneumopericardium. Note the fluid level.

Fig. 3.—Roentgenogram of chest taken six months after cessation of the effusion.

about ten days to two weeks. The effusion ceased in November, 1928. All aspirations were performed through the fourth or fifth interspaces, right or left, immediately adjacent to the sternum or one inch from it.

Laboratory Findings.—When the patient was admitted to the hospital the red blood cells numbered 4,350,000, the white blood cells 8,000, and the hemoglobin was 80 per cent. The differential count showed 58 per cent of polymorphonuclear cells and 43 per cent of lymphocytes. Throughout the course of treatment there was little variation in these figures. The urine usually was normal, although at times it contained a trace of albumin. The blood Wassermann and Kahn tests were repeatedly negative, as were the von Pirquet and intracutaneous tuberculin tests. Roentgenograms of the chest on numerous occasions showed the typical picture of a large pericardial effusion.

The aspirated fluid was clear and straw-colored, and on standing showed a few strands of fibrin. The specific gravity of this fluid was 1.016 to 1.018. It contained only from ten to twenty cells per cubic millimeter. These were chiefly endothelial cells with an occasional lymphocyte. Repeated cultures on various types of media were invariably negative, with the exception of one tube in which an organism of the colon group was found, obviously a contamination. On repeated occasions guinea-pig inoculation was negative for tubercle bacilli.

Course.—Many types of medication were tried. The patient was placed in bed and kept there for four months, after which time he was allowed to be up and take exercise in restricted amounts. He was given several toxic doses of salicylates and courses of Fowler's solution without any obvious improvement being noted. Novasurol was used on three occasions, after preparation with ammonium chloride, but aside from the fact that the interval between aspirations was increased by a few days, no benefit was noted. Generalized ultraviolet-light treatment was given and general supportive measures were instituted. A pneumopericardium was produced, 500 c.c. of air being introduced at one time. This was absorbed entirely within five days. Restriction of fluids was attempted but the pericardial effusion persisted despite apparent dehydration. The suggestion that some irritating fluid be introduced into the pericardial cavity was advanced on several occasions, and finally after forty-four aspirations had been necessary, 10 c.c. of a one-per-cent aqueous solution of aniline gentian-violet was injected, as suggested by Dr. A. R. Barnes of The Mayo Clinic and others. In twenty-four hours this was followed by fever, the temperature rising to 102.5° and the pulse rate to 130. There were evidences of large deposits of fibrin within the pericardium, and the symptoms subsided in a week. Four subsequent aspirations were necessary, decreasing amounts of fluid being drawn. The last aspiration was performed four weeks after the injection of the gentian-violet solution. Examination of the fluid removed after this injection proved it to be sterile and to contain a large quantity of fibrin and numerous polymorphonuclear leucocytes, as well as many red blood cells.

RESULTS

The striking feature of the case was the complete change in the patient's condition after the fluid had been removed by mechanical means. The formation of the fluid had been heralded by anorexia, lack of energy, a full feeling in the chest and abdomen, and frequently pain referred to the supraclavicular areas on each side. Paracentesis invariably gave immediate relief. During the year in which the patient was treated he increased in height and gained in weight, irrespective of the variations caused by the accumulation of fluid. After injection of the gentian-violet solution he experienced considerable

pain which was referred to the precordia but more especially to the shoulder areas, chiefly on the left side. After the cessation of fluid formation there was some persistent hepatic enlargement which gradually decreased until finally the liver returned to normal size. Cardiac examination now shows a normal-sized heart, with a regular, normal rate, and free from murmurs and evidences of *synechiae pericardii*. The patient is absolutely symptomless, and is living a normal life.

COMMENT

The etiological factor in the persistent pericardial effusion in this case can only be surmised. The absence of general constitutional reaction, the failure of specific drug therapy and the negative results of bacteriological investigation as well as the favorable outcome render it unlikely that at any time was an organism actually present in the effusion.

In the absence of any apparent cause it seems possible that the effusion was produced by some mechanical factor or pressure upon the inferior vena cava. Repeated studies by x-ray pictures failed to reveal any tumor of the thorax, pericardium or mediastinal structures, and the theory of a partial venous stasis in this locality cannot be confirmed. Theoretically its location would have to be within the very short course of the intrapericardial or superdiaphragmatic portion of the inferior vena cava. In experiments on animals Carl Rohde was unable to cause an effusion of pericardial fluid by placing stenosing ligatures on this vessel.

SUMMARY

A case of chronic pericardial effusion is presented which seems to be unique in the amount of fluid produced. The effusion probably was the result of some mechanical interference with the circulation of blood in the inferior vena cava or with the absorption of pericardial fluid. A chemical inflammation of the pericardium apparently resulted in relief of the etiological factor.

REFERENCE

- Rohde, Carl: Die Stauung der unteren Hohlvene vor dem rechten Herzer und ihre Bedeutung im Krankheitsbilde der Pericarditis adhaesiva. *Deutsche Ztschr. f. Chir.* 203-204: 18-41, 1927.

PAROXYSMAL CARDIAC PAIN IN A PATIENT WITH RHEUMATIC HEART DISEASE

HENRY S. DUNNING, M.D.
NEW YORK, N. Y.

PAROXYSMAL cardiac pain occurring in patients with rheumatic heart disease is infrequent. The case here described is that of a young adult who has been a patient of the First Medical Division of the New York Hospital and is reported, not only because it presents an unusual syndrome, but also for the reason that the pain, which was the first symptom of heart disease, has gained increasing dominance over thirteen years of exhaustive treatment.

CASE REPORT

J. S., a female, aged 26 years, was admitted to the hospital for the sixth time on October 22, 1930. In her previous history there was measles at the age of 2, confinement to bed for a month a few years later with whooping-cough, chicken-pox at 9, and 5 weeks in bed with bronchitis at 11 years. The pain of which she complained on admission was first experienced 13 years before at the age of 13 when, after jumping rope with playmates, she felt chilly, had no appetite for supper, and while relieving a thirst with water, was seized with a knife-like pain in the apical region of the precordia and a rapid beating of the heart; these symptoms continued for about 2 hours. Then followed a period of a month in bed with fever and pain in all of the joints. She attended school for a year, at the end of which occurred a second attack similar to the first. For 5 years she was afflicted with seizures of precordial pain, varying both in frequency and duration, until at the age of 18 she entered the hospital, presenting fever, joint pain, tonsillitis, and spontaneous precordial pain; the tonsils were removed. Two months later she was again admitted to the hospital because the pain was more frequent, especially at night. Rest in bed seemed to lengthen the intervals between the paroxysms. At about this time the pain first began to radiate from the apical region of the precordia to the right shoulder and entire right arm. Soon the attacks, occurring chiefly in the night, again became more frequent and necessitated a third period of rest in the hospital. After her discharge, fever and pain in the joints reappeared, the third invasion. The following year she again sought hospitalization and the rest in bed which had previously diminished the frequency and severity of the seizures. For the next four years she lived at home, attending the hospital out-patient clinic, and, with the exception of a few days during which her ankles were swollen and painful and of the continuous paroxysms of pain, she remained well. At the end of this period hospitalization was again required, for she was having intense pain at least 4 times a day. The pain at this time was so severe that it was finally decided to attempt to give relief by blocking of the nerve roots. The first to the eighth thoracic nerves on the left side were injected with alcohol by Dr. Swetlow,* and although after this procedure the attacks lessened

*Nerve injections were made on two occasions, the second to the seventh left thoracic roots the first time and the first, second, and sixth to the eighth left thoracic ganglia later. Following each, slight diminution of sensation to cotton and pin-point were detected in the skin of the left thorax. After the second blocking, ptosis, enophthalmos, and myosis of the left eye appeared, and the left arm felt subjectively and objectively warmer than the right; this phenomenon remained for a month.

in their frequency and intensity, it is probable that rest in bed alone was responsible for this result, as it had been before. If the blocking of the nerves had exerted any beneficial effect, it had disappeared 6 months subsequent to the last injections, because at that time the seizures of cardiac pain had increased not only in severity, but also to the number of 15 to 20 in the 24 hours, the majority taking place at night. The foregoing is a sketch of the history previous to the patient's sixth and most recent admission to the hospital.

A description of the syndrome as it has occurred most recently will now be given, first from the subjective standpoint of the patient, and then from the objective point of view of the observer. Precipitating causes of the paroxysms are numerous and varied. Primarily there is muscular exertion, such as walking rapidly and climbing stairs. Second, there are sudden changes in temperature, as produced by a cold draft of air and the swallowing of cold water. Third are the emotional reactions, when "my insides take a sudden jump." A knock on the door, a disagreement, an unpleasant dream, and exciting moving-pictures have all played their painful part. Finally there are those causes which we cannot name. Her field of activity, both physical and mental, is therefore greatly limited. The first sign of an attack is a sharp knife-like pain in the apical region of the precordia which radiates to the area of the third right intercostal space near the sternum and to the right shoulder and entire right arm. Shortly after the onset of the pain the heart pounds very rapidly. Accompanying these symptoms are a feeling of compression in the chest, shortness of breath, "lifelessness" of the right arm, weakness, dizziness, sweating, and great fatigue; after the seizure has spent itself the areas of pain remain sore. The patient believes that nitroglycerine and amyl nitrite, chiefly the latter, shorten somewhat the paroxysms, which last over periods varying from 3 minutes to 7 hours. The most promising form of treatment is prolonged rest in bed, which lessens both their frequency and their intensity. To the observer of these attacks the picture is one of a very pale young woman in a semirecumbent position in bed, arms limp at her sides, rolling frequently from side to side as if to shake off the pain which is clearly revealed in her face. There is rapid breathing and profuse perspiration. The neck bulges with each pulsation of the carotids and gives sufficient evidence of the tachycardia which is present, a rise of 48 beats to the minute above the normal in one instance. Blood-pressure determinations reveal an increase of tension, a rise of 30 points in the systolic pressure above the normal on one occasion, with no alteration in the diastolic. An electrocardiographic tracing taken during a seizure demonstrates a sinus tachycardia of 116 per minute, and a P-R interval prolonged to 0.22 seconds. There is a large Q-wave in Lead III and the T-wave is diphasic in Lead I. Another record obtained immediately after the subsidence of the paroxysm discloses frequent premature ventricular contractions and an inverted T-wave in Lead I.

Physical examination reveals a young adult female, Irish in origin, of excellent development and nutrition, pale of skin and lips, preferring the semirecumbent position in bed, but not orthopneic, throbbing slightly with each heartbeat, breathing quietly, with normal temperature, and not appearing ill, but showing in her face and mental attitude a resignation to a life of pain. The tissues over the carotids pulsate violently with the arteries. A heaving impulse may be seen and felt over almost the entire left chest, but no shocks or thrills can be detected. On auscultation over the precordia one hears in the region of the apex two murmurs: the first, entirely replacing the first heart sound, is of moderate intensity, blowing in quality, of moderate duration, and systolic in time; the second murmur is of moderate intensity, rumbling in quality, of short duration, and presystolic in time. Over the base are heard two murmurs: the first, most distinct in the first right intercostal space near the sternum and transmitted upward into the neck, is of loud intensity, rumbling in quality, of long duration, and systolic in time; the sec-

and murmur, most distinct in the second left intercostal space near the sternum and entirely replacing the second heart sound, is of loud intensity, blowing in quality, of moderate duration, and diastolic in time. The average resting rate of the heart is 84 per minute and the rhythm regular, but subject to premature ventricular contractions. An x-ray plate of the thorax reveals an enlarged heart, the greatest width to the left of the midline being 11.8 cm. and to the right 4.5 cm., the internal transverse diameter of the chest measuring 25.5 cm. Râles may be detected occasionally over the lung bases. The liver cannot be felt. There is a Corrigan pulse, a capillary pulse, and a pistol-shot sound on auscultation over the femoral artery. Blood-pressure readings taken in the absence of pain average 165 systolic and 51 diastolic. Edema has never been observed in the entire course of her illness. Electrocardiograms taken at periods when there was no pain show normal sinus rhythm, a wide and large P-wave, a wide and notched QRS group, inversion of the T-wave in Lead I, and a P-R interval prolonged to 0.22-0.24 seconds. These abnormal physical findings lead to the following diagnosis:

A (etiological). Rheumatic fever, inactive.

B (anatomical). Enlargement of the heart; cardiac valvular disease, aortic insufficiency and stenosis, mitral insufficiency and stenosis.

C (physiological). Regular sinus rhythm interrupted by periods of premature ventricular contractions and paroxysmal tachycardia; auriculoventricular partial heart-block; hypertension; anginal syndrome.

D (functional capacity). 2 b.

Of outstanding significance in this case of rheumatic heart disease is its most prominent symptom—paroxysmal cardiac pain, which not only marked the onset of the disease, but also has persisted with increasing vigor for thirteen years against a formidable array of procedures comprising the removal of focal infection, rest, nerve blocking, digitalis, quinidine, salicylates, analgesics, sedatives, antispasmodics, and vasodilators.

REFERENCES

- Schwartz: Paroxysmal Cardiac Pain, the Syndrome in Young Adults With Rheumatic Valvular Heart Disease. *AM. HEART J.* 2: 497, 1927.
White and Mudd: Angina Pectoris in Young People. *AM. HEART J.* 3: 1, 1927.
Levin: Angina Pectoris in a Child. *AM. HEART J.* 3: 495, 1928.

ACQUIRED RHEUMATIC PULMONIC STENOSIS AND INSUFFICIENCY*

SIDNEY P. SCHWARTZ, M.D.
NEW YORK, N. Y.

AND

DAVID SHELLING, M.D.
BALTIMORE, Md.

ACQUIRED rheumatic lesions of the pulmonary artery of sufficient severity to give clinical signs are very uncommon. There are exceedingly few cases reported in the literature where a diagnosis was suspected during the life of the patient and proved at autopsy.^{1, 2, 3} The following case is of particular interest, not only because of its unusual clinical manifestations, but also because of the typical radiographic findings associated with insufficiency of the pulmonary artery.⁴

REPORT OF CASE

M. R., a female, aged 22 years, was admitted to the Montefiore Hospital on April 29, 1928, and died on May 5, 1928. Her chief complaints were severe dyspnea, palpitation of the heart and swelling of the abdomen and lower extremities.

Previous Illness.—The patient became ill for the first time in January, 1921, and remained in bed for the next four weeks because of "inflammation of the lungs." She returned to work the following summer but was unable to walk. She became easily fatigued and unable to climb a single flight of stairs without stopping several times in order to "catch her breath." She entered the Bellevue Hospital where she remained at first, for three months, and during the subsequent two years she had to be readmitted to this institution on five separate occasions because of recurrent symptoms of shortness of breath, palpitation of the heart, precordial pain and swelling of the lower extremities.

In May, 1921, on her second admission to Bellevue Hospital, the patient suffered a hemiplegia. At that time, physical examination revealed a fairly nourished and fairly well developed young woman who was extremely short of breath. She showed a complete hemiplegia of the right side of the body. Her cheeks, lips and ears were very cyanotic. The superficial vessels of the neck were distended. There was marked pulsation of the carotid vessels. The heart was enlarged downwards and to the left, the apical impulse being in the fifth intercostal space in the anterior axillary line. In the second intercostal space, the left border of the heart percussed 6 cm. to the left of the midsternal line. There were a loud systolic and long rumbling diastolic murmur both best heard over the fifth intercostal space near the midclavicular line. A prolonged, loud diastolic murmur was audible over the second intercostal space to the left of the sternum. The murmur was well localized to this region but could also be heard distinctly over the upper left chest posteriorly. The pulses were equal and regular. The blood pressure was 120/80 mm. The lungs were clear, the liver edge was palpable two fingers below the costal margin. There was marked swelling of the lower extremities.

*From the Medical Division of the Montefiore Hospital for Chronic Diseases, New York City.

X-ray examination at that time is summarized as showing "an enlarged heart with a straightened left border and a small bulge of the pulmonary artery."^{*}

Because of the absence of peripheral signs of aortic insufficiency such as a Corrigan pulse, a low diastolic blood pressure and capillary pulsation, a diagnosis of pulmonary insufficiency was made at this time in addition to the evident stenosis and insufficiency of the mitral valve.

With adequate rest and the judicious use of diuretics, the patient was able to leave the hospital in a fair condition within four weeks after admission. However, within the next few months, she became progressively worse and because of the extreme shortness of breath and palpitation of the heart, she had to be readmitted to this institution several times in the succeeding two years. That was in 1921.

The patient remained at home from 1924 to 1927. In the winter of 1927, she entered the Jewish Hospital of Brooklyn in a very critical condition. In the two or three weeks prior to her admission to that institution she was having dizzy spells, vomiting, headaches, and a progressive increase in the swelling of the legs and ankles.

On examination, she was found to be extremely dyspneic and orthopneic and showed signs of dropsical effusion in the abdominal cavity with marked generalized swelling of practically the entire body. Her heart rhythm was totally irregular, and averaged 120 beats per minute, there being a pulse deficit of 28. The liver was now at the level of the umbilicus and was pulsating. The unusual clinical features were the wide areas of pulsation in the second and third intercostal spaces to the left of the sternum. In this region, the left border of the heart percussed near the anterior axillary line. A short, rough systolic thrill with a sharp diastolic shock could be felt over the second intercostal space near the midclavicular line. The apex of the heart presented a loud systolic murmur and a short rough rumbling diastolic murmur.

The x-ray film of the chest taken on January 31, 1927, revealed the heart shadow to be somewhat pyramidal in contour, with a rounded apex, and decidedly broadened inferiorly with displacement towards the left. The findings were considered atypical, and from the radiograms alone it was impossible to diagnose the type of valvular defect. The lung fields were clear with the exception of the right base which presented slightly increased markings and change in appearance when the patient was in the erect posture as compared with the prone position, suggesting the presence of a small amount of fluid.[†]

Because of the unusual clinical findings with the marked enlargement and pulsation of the heart in the second intercostal space, in the absence of large quantities of fluid in the right pleural cavity, a diagnosis was ventured of aneurysm of the pulmonary artery associated with chronic valvular heart disease of the mitral orifice, complicated by a relative tricuspid insufficiency.

Between her discharge from the Jewish Hospital of Brooklyn and her admission to the Montefiore Hospital, the patient had one paracentesis abdominalis.

Physical examination at the Montefiore Hospital on April 29, 1928, revealed an intensely dyspneic and orthopneic young woman who was acutely ill. Her face showed pale cyanosis in marked contrast with the intense cyanosis of her hands and feet. She was in a sitting posture but her superficial and deep neck veins were markedly distended, the latter showing a ventricular form of venous pulse. There was a slight deformity of the anterior left side of the chest with bulging of the left half of the sternum and the costosternal junctions in the region of the second, third, fourth, and fifth intercostal spaces. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. There was a marked

^{*}We wish to express our thanks to Dr. M. J. Thornton of Bellevue Hospital for the privilege of this report.

[†]We wish to express our thanks to Dr. John A. Daugherty for the privilege of using this report.

precordial heave with a diffuse pulsating wave from the third to the fifth intercostal spaces. This part of the chest was painful to touch. The area of cardiac dullness was enormously enlarged to the left reaching the anterior axillary line in the second and third left intercostal spaces. A marked systolic pulsation over the second intercostal space extended 12 cm. to the left of the midsternal line. Over this region but nearer to the sternum, there was a marked systolic thrill felt best with the patient in a sitting posture and leaning slightly forward and to the left.

The apical region of the heart presented a loud systolic and a short, rough, rumbling diastolic murmur, while the basal region of the heart on the left side in the second intercostal space revealed a short, rough systolic murmur with a loud prolonged diastolic murmur. P_2 was not audible. The heart rate was totally irregular, and there was clinical and graphic evidence of auricular fibrillation. Both pleural cavities revealed the presence of small quantities of fluid. The liver edge was at the level of the right iliac crest, and the legs were extremely swollen. There was a small quantity of fluid in the abdominal cavity.



Fig. 1.—Roentgen-ray examination of the chest on admission to the Montefiore Hospital revealed a moderate amount of fluid in the right pleural cavity. The heart was enlarged and rotated so that the aortic knob was not visible in the anteroposterior position. There was an unusual dilatation of the pulmonic artery which formed the first curve on the left side of the heart shadow.

Roentgen-ray examination of the chest revealed the heart shadow to be pushed over to the left by a small effusion in the right pleural cavity. (Fig. 1.) The heart was enlarged and was rotated so that in the anteroposterior position the aortic shadow was not visible. The first curve of the left border of the heart was formed by a markedly dilated and prominent pulmonic artery. The unusual dilatation and pulsation of the pulmonic artery were best seen in the right oblique position. In this plane the left auricle was seen to be extremely dilated and to encroach upon the retrocardiac space. The angle at the bifurcation of the trachea was straightened out. The aortic shadow was barely visible. Both the right and left ventricles were enlarged, but no roentgenographic evidences of pericardial effusion could be made out.

The electrocardiogram revealed good voltage with a right ventricular predominance and auricular fibrillation. (Fig. 2.)

On May 1, 1928, a thoracentesis of the right pleural cavity yielded 1300 c.c. of clear yellowish fluid. Two days later, a similar amount of fluid was removed from the same side of the chest. In performing the second operation the puncture needle was inserted to the inner side of the angle of the right scapula and 40 c.c. of a turbid, dark, yellowish fluid was removed at first which, because of its distinctly different opacity, was thought to have come from the pericardial sac. A second procedure at this time with the needle inserted to the outer side of the right scapula in the seventh intercostal space yielded a clear, straw colored fluid. The cultures of all the fluids were sterile.

The pulsations previously observed in the second and third intercostal spaces became more prominent, each systole resulting in the development of a slight aneurysmal bulge in these intercostal spaces that extended from the left border of

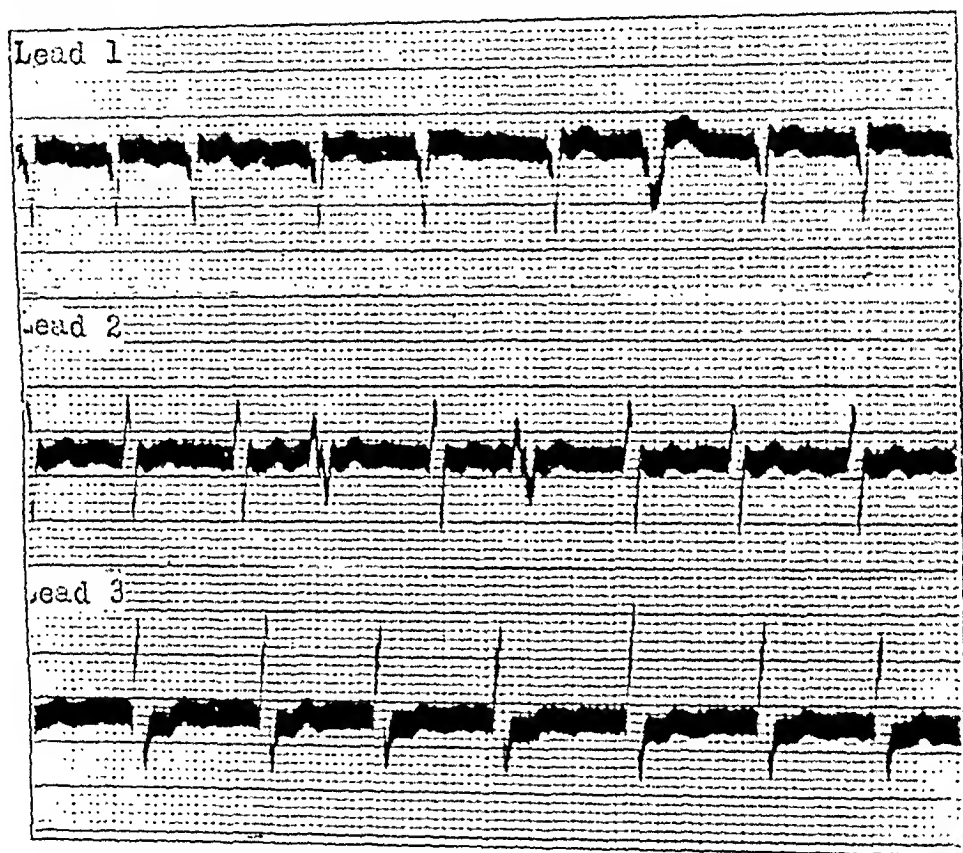


Fig. 2.—The electrocardiogram revealed right ventricular predominance and auricular fibrillation with many aberrant ventricular complexes.

the sternum to the axillary region. The systolic thrill over this region was rougher and more pronounced. Both the systolic and diastolic murmurs heard over this area were now very loud, the former being very rough and the latter softer in quality and occupying all of diastole. Both of these thrills and murmurs were different in quality and character from those audible at the apical region. The heart rate was totally irregular and there was a pulse deficit of 24. The blood pressure was 100/80 mm. There were no peripheral signs of aortic insufficiency such as a Corrigan pulse or capillary pulsation of the fingers.

The x-ray examination of the chest at this time showed signs of pleural effusion at the right base extending up to the fourth rib posteriorly. The heart was markedly enlarged, the left border almost reaching the lateral wall. The right cardiac border was obscured by the overlying shadow. The aorta was not visible

at all in the anteroposterior position. There was an increase in the size of the pulmonic artery as compared with the previous plate.

On May 5, 1928, at about 6 P.M., the patient became very listless and shortly thereafter, comatose. She died at 2 A.M. of that day. A post-mortem pericardial tap at the level of the third intercostal space 4 cm. to the left of the sternum yielded only 40 c.c. of slightly turbid yellowish fluid.

Autopsy Findings.—The autopsy was performed by Dr. Bernard Seligman six and a half hours post-mortem.

A post-mortem radiographic examination of the chest with the body in a sitting posture revealed the presence of small quantities of air in both pleural cavities. The main bulge of the heart extending on the left upper border from the third intercostal space to the clavicle was well defined and recognized as a largely dilated pulmonic artery.

The incision was unfortunately limited so that it was impossible to correlate exactly the position of the heart *in situ* with the radiographic findings.

The heart weighed 600 gm.

The parietal pericardium was free from the surrounding tissues. The visceral surface of the pericardium over the right auricle was thickened and covered for a distance of about 2×1 cm. by fresh fibrinous exudate. There were no adhesions between the visceral layer of the pericardium and the heart.

The cavity of the right auricle was markedly enlarged. Its trabeculae carneae were prominent and hypertrophied, and its endocardial surface was smooth throughout. The thickness of the wall was from 1 to 1.5 mm.

The cavity of the left auricular appendage was about five times the normal size and contained several thrombi.

The cavity of the left auricle was markedly enlarged. Its endocardial surface was smooth and glistening but of a grayish color. There were a few small, slightly raised, yellowish white areas near the mitral surface. Its wall was thickened and measured 2 mm.

The cavity of the left ventricle was markedly dilated, and its wall measured 1 cm. at the apex and 2 cm. near the papillary muscle. The papillary muscles were markedly hypertrophied and covered by a white, smooth, glistening surface. The chordae tendineae were of a pearly white color and remarkably thickened, shortened and fused.

The cavity of the right ventricle was tremendously dilated. Its endocardial surface was smooth and glistening. Its wall measured 5 mm. in the region of the pulmonic cone, and 3 mm. in the region of the tricuspid ring. Its endocardial surface near the pulmonary orifice in the region of the right posterior cusp presented a thickened, pearly white area measuring 1 cm. in diameter with a crescentic superior surface appearing as a redundant fold fusing with the under surface of the cusp.

The pulmonic ring was markedly dilated and measured 7.75 cm. (Fig. 3.)

The left posterior and anterior cusps of the pulmonary valve were fused together on their contiguous borders. For a short distance in this region, there were two distinct folds of the valve margins which were not in any way different in consistency from the remainder of the valves. These presented a small triangular depression between them. The two margins of the valve were fused near the insertion of the cusps. The free borders of the cusps were thickened and rolled inwardly but showed no vegetations.

The free border of the right posterior cusp presented almost in its entirety a large, thick firm mass of agglutinated calcified nodules which were contiguous with a similar area of a large and uniformly hardened nodule on the endocardial surface of the right ventricle adjacent to them. On section, these were sclerotic, calcified, grayish yellow in color and extended to the base of the cusp almost obliterating the entire sinus. (Fig. 4.)

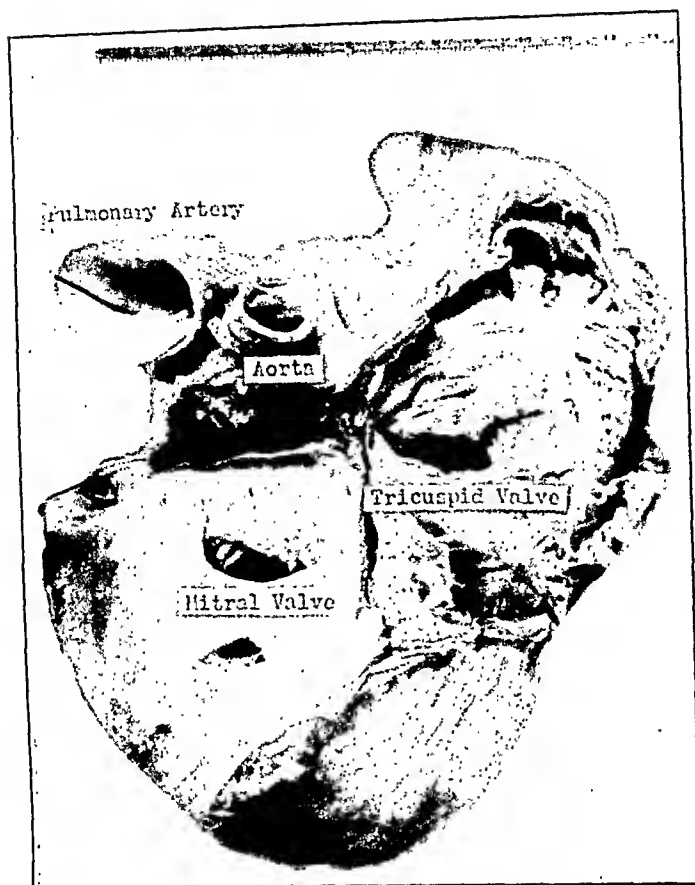


Fig. 3.—The heart shortly after its removal from the thoracic cavity showing the unusual dilatation of the pulmonary artery beyond the pulmonary ring. Compare its diameter with that of the aorta.

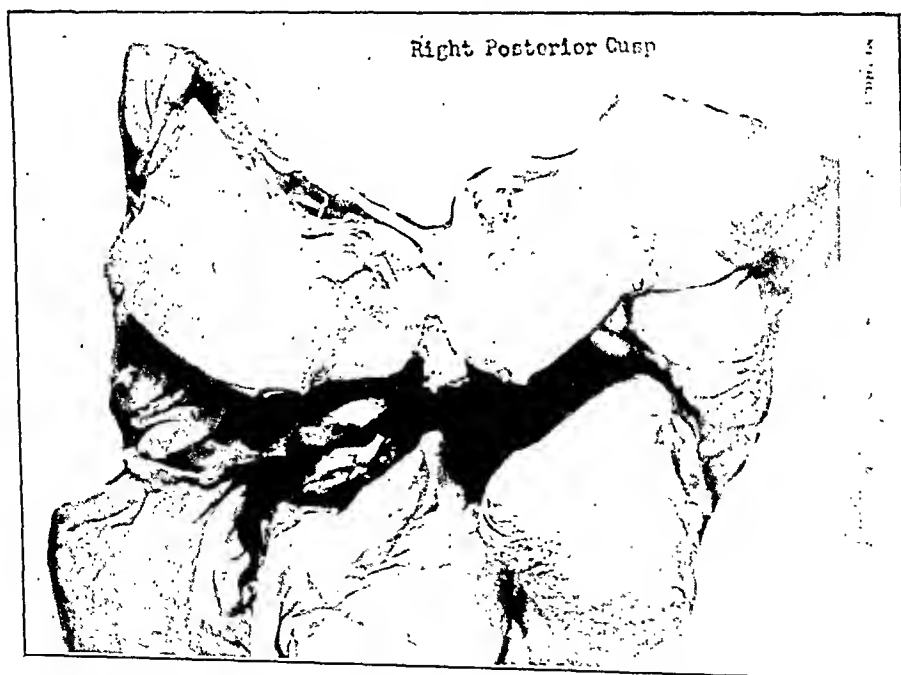


Fig. 4.—The bicuspid pulmonary valve showing rheumatic valvulitis of both valves with inward rolling of the hard firm edges and a large calcified agglutinated mass covering the anterior surface of the right posterior cusp.

The pulmonary artery above the pulmonary valve was wider than the pulmonic ring, measuring in this region 8.75 cm. Its surface presented few small, soft, raised, yellowish plaques.

The mitral valve admitted the tips of two fingers. The free borders of both leaflets were markedly thickened, rolled inwardly and white in color and on the atrial surface showed marked indentations which felt very hard and were sclerotic. Both leaflets presented numerous small fresh vegetations which were conglomerant and in part calcified. Throughout the entire aortic leaflet of the mitral valve, but particularly nearer the mitral ring, there was a small area measuring 2 cm. \times 2.5 cm. of a firm calcified mass which was thickened over a distance of about 4.5 cm. In one area the endocardium was denuded and exposed this translucent material. The outer leaflet showed thickening and was pearly white in color.

The tricuspid orifice was moderately dilated. The valves were thin and pearly white in color and the thin free edges were slightly thickened and rolled inwards. The ring measured 10.5 cm.

The aortic ring measured 6 cm. The cusps were well preserved and thin. There were no vegetations present. None of the leaflets were thickened.

The aorta showed a few small, soft, raised, yellowish plaques.

The coronary vessels were slightly thickened and showed raised, diffuse, confluent, small yellowish plaques.

DISCUSSION

The interesting lesion in this patient as revealed by the autopsy findings, in addition to the evident mitral and tricuspid lesions, is an acquired rheumatic valvulitis superimposed on a malformation of the pulmonic valves which in this case consisted of absence of one of the pulmonic leaflets. This underlying congenital malformation may explain the unusual dilatation of the pulmonic artery for so long a period since the first diagnosis of pulmonic insufficiency was made seven years prior to her death; for it is well known that such congenital defects of this artery may produce an insufficiency of the valves even in the absence of any acquired disease.⁵ It is very likely, in view of the rarity of acquired rheumatic lesions of the pulmonic artery, that the congenital malformations were responsible in part for the localization of the rheumatic virus on the pulmonic leaflets.

The characteristic roentgen-ray picture of pulmonic insufficiency, as described by one of us⁴ in a previous communication, was of great help in the diagnosis of that particular lesion whereas the stenosis of the valves was suspected solely from the clinical evidences which in the main were the rough systolic thrill and localized murmurs in the region of the second intercostal space to the left of the sternum.

REFERENCES

1. Paul, C.: Du rétrécissement de l'artère pulmonaire contractée après la naissance. *Union Méd.* 3: Sec. 12, 1871.
2. Rinsema, Th.: Ein Fall von acquirirter Stenose des Ostium Pulmonale. *Deutsches Arch. f. klin. Med.* 24: 216, 1884.
3. Gerhardt, D.: Ueber Schliessunfähigkeit der Lungenarterienklappen. *Charité Ann.* 1: 92, 1892.
4. Schwartz, S. P.: The Radiographic Signs of Pulmonic Insufficiency. *AM. HEART J.* 2: 407, 1927.
5. Grawitz, E.: Zwei seltne Fälle von Inkontinenz des Ostium Pulmonale bedingt durch Fehler eines Klappensegels. *Virchows Arch. f. path. Anat.* 110: 426, 1897.

Department of Reviews and Abstracts

Selected Abstracts

Gross, Louis, Antopol, William, and Sacks, Benjamin: A Standardized Procedure Suggested for Microscopic Studies on the Heart. *Arch. Path.* 10: 840, 1930.

The authors have developed a procedure for cutting blocks of heart muscle tissue which show a maximum number of lesions in a minimum number of blocks. The six blocks include the four valves, the four valve rings, the pericardium of the left and right sides, the heart, the left and right auricles, the myocardium of the left ventricle, right ventricle, interventricular septum and left posterior papillary muscle; the bases of the aorta and pulmonary artery; the pericardial wedges abutting against the valve rings; the neuromuscular bundle, and the coronary sinns.

It is pointed out that the myocardium in practically every section is taken from a site where the vessels can be considered end vessels. It is probably for this reason that early vascular changes and their results are so frequently observed in these sections, and that inflammatory lesions, which may possibly owe their localization to the fact that the vessels in this region are terminal, are so frequently found here.

By using these sections only, the authors have been able to find Aschoff bodies in 90 per cent of 40 hearts showing acute verrucous endocarditis and in 15 per cent of 39 hearts showing chronic valvular disease. In some of the hearts not showing these lesions, sections from other parts were taken as well, but failed to show Aschoff's bodies.

Middleton, William S., and Oatway, William H.: Insulin Shock and the Myocardium. *Am. J. M. Sc.* 131: 39, 1931.

The authors have studied the changes occurring in the heart of 11 patients during insulin shock. They have observed the establishment of common changes in certain of the component waves of the electrocardiogram and to less common but more serious errors in conduction during insulin shock.

Because of the gravity of the changes noted in the presence of myocardial lesions, particular caution is enjoined in the use of insulin in such patients. Where any question exists, the avoidance of hypoglycemia must be insured by an adequate coverage of insulin through concomitant intravenous glucose injections even though there is no agreement as to the causal relationship of the depressed blood sugar.

Hurxthal, Lewis M.; Menard, O. J.; Bogan, M. E.: The Size of the Heart in Goiter. A Teleroentgenographic Study. *Am. J. M. Sc.* 180: 772, 1930.

Teleroentgenograms were made on one hundred consecutive cases of toxic and one hundred consecutive cases of nontoxic goiter. No definite relationship could be found between the duration of the disease or weight loss and the size of the heart. Cardiac enlargement as determined by teleroentgenography showed a fairly direct relationship to age and coincident cardiovascular disease.

The number of enlarged hearts of different degrees was practically the same in both toxic and nontoxic goiter.

The authors conclude that if hyperthyroidism causes cardiac enlargement or hypertrophy and dilatation, it is slight.

Cotton, Thomas F.: The Treatment of Mitral Disease in Children. *Brit. M. J.* 1: 481, 1931.

The author has selected the first one hundred boys admitted to a convalescent cardiac home in the years 1919 to 1922 with rheumatic heart disease. The after histories of all but six of these have been obtained after seven years in one group and eight years in another. All have had rheumatism or chorea and all but two have had signs of a rheumatic infection of the heart. Fifty-seven were diagnosed as having mitral disease, twenty-three mitral stenosis, fourteen mitral stenosis and aortic regurgitation and four had aortic regurgitation alone.

The author believes that mitral disease in children is probably always associated with a rheumatic invasion of the myocardium and is evidence of carditis. At the end of seven years, 17 or 29 per cent were dead. Fifteen of those with mitral stenosis or 65 per cent were dead after 8 years. In the smallest group there were 14 cases of mitral stenosis and aortic regurgitation, six of whom were dead after 8 years.

From a study of this group it seems permissible to state that the prognosis in children with mitral stenosis over a period of eight years who have had careful treatment in a special convalescent home is a grave one. They raise the question of this form of treatment in mitral stenosis and whether it is worth while treating such cases in a special convalescent home.

The treatment of children with chronic rheumatism is unsatisfactory when they belong to the poorer classes. On leaving the convalescent home where they have been more or less protected against reinfection they return to unhealthy homes and are again exposed to rheumatic and other infections which cause more damage to the heart muscle and valves. The children of well-to-do persons are better protected against the ravages of rheumatism for they have home surroundings in which they can live, grow up and be educated under conditions which are comparable to those which exist in a special convalescent home. The prognosis is more favorable in these children because the disease is likely to be recognized in its early stages and suitable treatment given at a time when it is possible to prevent the development of progressive changes leading to a serious cardiac disability.

Slater, Solomon R.: The Involvement of the Coronary Arteries in Acute Rheumatic Fever. *Am. J. M. Sc.* 181: 203, 1931.

Three cases of adults with acute rheumatic fever are cited in detail which showed electrocardiographic evidence of coronary arterial involvement. The diagnosis of acute coronary closure was also suggested strongly by the symptoms of collapse, pericardial friction rub, leucocytosis and fever. It seemed that in all three cases the endocardium received practically none of the brunt of the attack of the rheumatic virus. All three patients recovered.

It is emphasized that during an acute rheumatic infection any blood vessel, large or small may possibly be involved and that those of the heart may likewise be involved; that when the larger coronary branches are affected under certain circumstances it may be sufficient to encroach so upon the lumen as to occlude it; or a thrombus may occur secondarily producing a closure. When the closure occurs, the patients experience excruciating pains indicative of the lesion.

Parsonnet, Aaron E., and Hyman, Albert S.: Heart Sound Failure. A Phonocardiographic Study of This Phenomenon in Acute Coronary Occlusion. *J. A. M. A.* 96: 1124, 1931.

In a series of fourteen cases of acute coronary thrombosis in which heart sound failure had been a conspicuous feature, graphic methods of study have been employed. In eleven of these there have been uniform phonocardiographic alterations in the sounds. The authors believe that heart sound failure may be regarded as one of the pathognomonic signs of coronary thrombosis and when the diagnosis is rendered uncertain by the predominance of symptoms apparently arising from other sources, the discovery and recognition of this characteristic impairment of tone quality may go far to clear up the problem at hand.

Proger, Samuel H.: The Electrocardiogram in Obesity. *Arch. Int. Med.* 47: 64, 1931.

The electrocardiogram of the obese person with an apparently normal heart in a large percentage of cases shows left axis deviation, flattening or inversion of the P-wave; inversion of T-wave in Lead III. In those cases in which the heart appears to be normal there are no significant changes in the T-wave in Leads I and II, regardless of the extent of the axis deviation. Left axis deviation due to change in position is usually associated with inversion of the T-wave in Lead III, whereas left axis deviation owing to relative left ventricular hypertrophy is commonly associated with an erect T-wave in Lead III.

Cases of obesity without other organic disease show approximately the same incidence and extent of left axis deviation as cases of obesity complicated by hypertension and cardiac enlargement. Axis deviation in electrocardiogram of the obese patient is of no value as an aid in the diagnosis of relative ventricular hypertrophy.

There appears to be a general relationship between the anatomic angle of the heart as measured on the orthodiagram and the electrical angle as calculated from the electrocardiogram.

Factors such as age, sex, duration and percentage of overweight beyond 25 per cent seem to have no definite relation to changes in the electrocardiogram.

Hill, Ian G. W.: Bundle Branch Block. *Quart. J. Med.* 23: 15, 1930.

Forty-one cases of bundle branch block with clinical findings are recorded. A diagnosis of this condition by means of physical signs alone is not feasible. No demonstrable change in the ventricular complexes could be produced by therapeutic doses of atropin and digitalis.

The right branch of the bundle was traced by serial sections in two cases which during life showed the features of right bundle branch block. In both, and in one child's heart cut as a control the right branch was formed to split up or lose its identity at a higher level than was expected from anatomical teaching. In one case in addition to widespread fibrosis of the myocardium which did not involve the bundle or its branches foci of round celled infiltration were demonstrated in the main stem and in the right branch. From their nature and from the known syphilitic element in the case, these foci are thought to be possibly of a specific origin.

The question of "incomplete bundle branch block" has been considered and it is urged that this term be not applied to cases yielding an incomplete electrocardiographic picture of bundle branch block but solely to cases which show analogy to incomplete block of the main stem, i.e., delayed conduction.

Beresford, E. H., and Earl, C. J. C.: Spontaneous Cardiac Rupture. A Review of Forty-Six Cases. *Quart. J. Med.* 23: 55, 1930.

Forty-six cases of spontaneous cardiac rupture are reviewed and discussed. Recent acute infarction of the heart is considered to be almost invariably the underlying cause.

The incidence in this group increased with advancing years, the highest figure being reached in the eighth decade. In this group of cases after making allowances for errors in grouping, the cases occurred in the ratio of about four females to one man. This opposes the view determined from previous similar series of cases. The frequent association of insanity with cardiac rupture is remarkable.

Mechanism of the rupture is discussed and the importance of excessive fat, of softening and of hemorrhage as factors is emphasized.

Stewart, Sloan G.: Problems of Cardiac Disease Associated with Urinary Retention. *Am. J. M. Sc.* 181: 362, 1931.

There is a group of cases in which lower urinary tract obstruction and evidences of cardiac disease are commonly associated. That this may be of primary importance, from a therapeutic standpoint, is illustrated by clinical reports of two cases. The need of adequate urological histories and examinations in the medical studies on all male patients is emphasized. A brief statistical review of forty cardiac cases with prostatic obstruction reveals cardiac arrhythmias in a large percentage of cases and widespread arteriosclerosis and coronary sclerosis of an unusually advanced type. Two cases are reported of myocardial failure refractory to rest and digitalis in which bladder retention without obstruction was discovered. The results of constant bladder drainage as a therapeutic measure are discussed. The determination of prognosis of these cases and the evaluation of infection as a complication of catheter drainage are difficult problems which are briefly presented.

Andersen, Maine C.: Paroxysmal Ventricular Tachycardia. *Am. J. M. Sc.* 181: 369, 1931.

A case of paroxysmal ventricular tachycardia in which there was no evidence of serious heart disease is reported with electrocardiographic records. The author believes that the slight displacement in the auriculoventricular rhythm in paroxysmal ventricular tachycardia is sufficient to cause the cyclic accentuation of the first sound at the apex.

It is suggested that in paroxysmal ventricular tachycardia occurring in an individual—not the subject of demonstrable heart disease—there is not only an inherited sensitive nervous system but also an inherited cardiac neuromuscular aberration.

Parkinson, John, and Campbell, Maurice: Paroxysmal Auricular Fibrillation. *Quart. J. Med.* 23: 67, 1930.

This paper is based on the notes of 200 patients who had paroxysms of auricular fibrillation. It is believed that the cases can be divided into three groups; one, typical recurrent paroxysms which form more than one-half of the cases in this group; two, a few paroxysms preceding the onset of established fibrillation; three, single or very occasional paroxysms often of longer duration seen in the case of congestive heart failure, after coronary thrombosis, with infections such as pneumonia or with no apparent cause.

During the immediate attack, the prognosis is excellent but if the attack lasts more than several days permanent fibrillation becomes much more likely and after

two weeks is almost certain. Seventy per cent of the cases studied showed signs of structural heart disease. The symptoms usually were not severe. With a longer attack or where the heart was already in difficulty all the signs and symptoms of congestive heart failure were seen.

Master, Arthur M.: Low Voltage T-Waves in the Electrocardiogram. *Am. J. M. Sc.* 181: 211, 1931.

In 107 patients a study was made of low voltage T-waves in which the amplitude in any lead was not more than 1 mm. In 12 patients that were examined post-mortem all showed definite myocardial or pericardial damage. Another group of 12 patients died but no autopsy was performed. Eleven died with typical myocardial failure and 1 of pulmonary tuberculosis.

Altogether, there were 89 hospital patients with flat T-waves, the mortality among those with degenerative cardiovascular disease was at least 44 per cent during the course of a three to four years' investigation.

Acute rheumatic infection of the myocardium or pericardium often produces a flat T-wave and in the progression of the disease the T-wave may become inverted or if the patient recovers, it will become upright. The rheumatic cardiac patient with a flat T-wave is acutely ill and is probably always a bed patient. The so-called coronary T-wave or cove-plane T-wave that is customarily associated with coronary artery occlusion may appear in a patient with rheumatic pericarditis. Suggestive evidence is presented that pericarditis alone without disease of the underlying myocardium, may cause a flat T-wave. When a flat T-wave appears in the course of other diseases it seems to indicate a very severe form of illness. These T-waves are practically always transitory becoming inverted as the myocardial or pericardial damage spreads and increasing in amplitude on cure or improvement.

Parkinson, John, and Bedford, D. Evan: Electrocardiographic Changes During Brief Attacks of Angina Pectoris. *Lancet* 1: 15, 1931.

In 5 patients with attacks of angina pectoris electrocardiograms taken during short paroxysms show definite and transitory changes in the ventricular deflections. There was a depression of R-T and a diminution in the amplitude or inversion of the T-waves in one or more leads, changes closely resembling though not so pronounced as those which follow cardiac infarction in the early stages. It is surely significant that both transient anginal pain and cardiac infarction can affect the electrocardiogram in a similar manner; and it seems reasonable to infer that the mechanism underlying this electrocardiographic change is essentially the same in both cases—an ischemia of a part of the cardiac muscle.

The authors do not suppose that the electrocardiogram is always modified during short anginal attacks but their evidence suggests that it is modified in a proportion of cases.

Levy, Robert L.: Mild Forms of Coronary Thrombosis. *Arch. Int. Med.* 47: 1, 1931.

A group of eight cases is reported as exemplifying mild forms of coronary thrombosis. The records of these patients appear to define a distinct clinical group characterized by the relative youth of the patients and rapid rate of recovery both subjective and objective. One of the eight patients died of a second attack; one patient had a second occlusion one year after the first; another has had two later attacks; restoration of function has been complete in two patients; two of the patients are free from symptoms on restricted activity; three have symptoms even with carefully regulated lives; two still complain of pain in the heart and one of dyspnea on effort.

It is believed that this condition frequently is not recognized because of the atypical clinical picture. Although a rapid rate of recovery tends to indicate a favorable outcome of the immediate attack, accurate prognosis as to the liability to recurrence and life expectancy is extremely difficult.

Wood, Francis C., and Wolferth, Charles C.: *Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion.* Arch. Int. Med. 47: 339, 1931.

Thirty cases of angina pectoris were studied electrocardiographically before, during and after their attacks. Fifteen showed temporary ventricular complex changes during the pain, which probably cannot be explained by the exercise which produced the attacks nor by the changes in blood pressure and pulse rate which accompanied them. The remaining fifteen showed no specific electrocardiographic changes during their attacks. The severity of the pain did not seem to be the main factor that determined the presence or absence of "specific" electrocardiographic change during an attack. The relief of anginal pain by nitrites does not always seem to be dependent on the drop of blood pressure which this group of drugs produces. The prognostic importance of specific electrocardiographic changes during attacks has not as yet been determined. Although there were no untoward occurrences in this series of cases, the authors are not prepared to recommend the electrocardiographic procedure described as a diagnostic test in angina pectoris.

In a series of dogs and cats temporary interference with a part of coronary occlusion produced temporary and rapidly reversible changes in the electrocardiogram somewhat analogous to those seen during attacks of angina pectoris.

The factors that seem of importance in the production of these changes were: (1) the vessel that was occluded; (2) the size of the area of the myocardium the blood supply of which was interrupted; (3) the state of the heart before the vascular occlusion; (4) the duration of the occlusion and (5) possibly the simultaneous obstruction of accompanying veins.

Experimental temporary coronary occlusion frequently produced no electrocardiographic change, therefore the absence of specific electrocardiographic change in fifteen patients during attacks of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur. In experimental coronary occlusion, cardiac arrhythmia which could be attributed to the circulatory disturbance in itself was not a frequent early phenomenon. When it did occur it seemed to be attributable to mechanical stimulation of the heart muscle by the mechanism producing the occlusion.

The evidence presented is in accord with the hypothesis that the majority of attacks of angina pectoris are associated with a localized circulatory disturbance of the heart. It does not rule out the possibility that other mechanisms may produce paroxysms of precordial or substernal pain.

Findlay, Leonard, MacFarlane, James W., and Stevenson, Mary M.: *Rheumatic Pericarditis in Childhood.* Arch. Dis. Child. 5: 1, 1930.

The authors have studied the records of 51 examples of rheumatic pericarditis admitted to the Royal Hospital for Sick Children, Glasgow, between 1915 and 1928 inclusive. Of thirty post-mortem examinations in children dying from all forms of rheumatic heart disease, there were implications of involvement in the pericardium in 50 per cent. In two of the cases pericarditis apparently was the sole cardiac lesion, 44 of the 51 patients had suffered at some time or another from arthritis,

15 of the patients had suffered from chorea but 13 of them had also had arthritis so that in only 2 children was chorea the sole other rheumatic manifestation than the cardiac involvement. Thirty-two cases were females and 19 males. Of the 51 cases 26 died, 24 during acute phase of the disease and 2 at a later date from cardiac decompensation. Of the 25 cases still alive, there was one with neither signs nor symptoms of cardiac disease; in 7 cases there are signs of cardiac disease but no symptoms; in 9 there are definite symptoms of cardiac disability as well as signs and in 3 the disability is extreme.

Sutton, Lucy Porter: Pericarditis with Effusion. *Am. J. Dis. Child.* 41: 78, 1931.

The object of this paper is to call attention to the pulmonary signs associated with moderate and large pericardial effusion. Several cases are reported together with x-ray illustrations and charts describing the signs.

The posterior site for tapping the pericardium is described. It is believed to be perfectly safe and one is far more certain of reaching the fluid than in using the points formerly recommended. Although only one of these cases seemed to require relief because of the size of the effusion, it appears possible that removal of some of the fluid may hasten absorption and thus lead to quicker recovery.

Wood, Francis C., and Eliason E. L.: Rheumatic Peritonitis. *Am. J. M. Sc.* 181: 482, 1931.

A patient with a past rheumatic history and a well-marked rheumatic cardiac lesion developed lower abdominal pain, diarrhea and signs of peritoneal irritation. Operation disclosed an abundance of clear fluid in the peritoneal cavity and an acute serositis and subserositis of the peritoneum of unknown etiology. Nine days after operation acute pericarditis developed and after a stormy course of typical cardiac rheumatism of six weeks' duration the patient died.

It seems worth while to bear in mind the possibility of rheumatic peritonitis in the differential diagnosis of abdominal pain where it occurs in a patient with signs of present or past rheumatic fever.

Scott, L. C.: The Potassium Content of the Hearts of Persons Dying from Edematous and Nonedematous Conditions. *Arch. Int. Med.* 47: 116, 1931.

In a series of 69 analyses of cardiac muscle for inorganic constituents special attention was paid to the potassium and sodium in 32 hearts from patients who had died from a variety of diseases. Fourteen of these patients showed edema of a greater or lesser degree and of varying periods of duration and eighteen were free from it. The results do not seem to indicate that there is on an average any appreciable difference in the amount of these elements in hearts from edematous and from nonedematous patients.

There is considerable variation in the amount of potassium and sodium in hearts regardless of whether the disease processes from which the patients died were or were not productive of edema. The percentage of sodium may be greater than that of potassium and vice versa without any apparent relation to disease.

Demonstration of potassium in cardiac tissue by Macallum's sodium cobalttrinitrite method indicates that the larger proportion of the salts is contained in the fluid bathing the muscle cells, and that they are rather uniformly diffused throughout the protoplasm.

Calhoun, J. Alfred, Cullen, Glenn E., Clarke, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. VI. The Effect of Overwork and Other Factors on the Potassium Content of the Cardiac Muscle. *J. Clin. Investigation* 9: 393, 1930.

The water content of the ventricular muscles of subjects dying of congestive heart failure was not significantly increased. Patients dying with acute and extensive disease of the lungs had diminished potassium content of the right ventricle but not of the left ventricle. When myocardial insufficiency results in pulmonary congestion, the potassium content of the left ventricle is diminished. When myocardial insufficiency results in hepatic and systemic edema, the potassium content of the right ventricle is decreased. If both systemic and pulmonary congestion were present, both ventricles were poor in potassium. The cardiac potassium was not diminished in a subject with coneretio cordis and myocardial atrophy. The dilated ventricles were poor in potassium; the ventricles which were hypertrophied but not dilated showed variable results.

The authors believe that edema is not the cause of loss of cardiac potassium; they believe that overwork causes loss of potassium from heart muscle and this loss is one of the predisposing factors to cardiac fatigue and failure.

Calhoun, J. Alfred, Cullen, Glenn E., and Harrison, T. R.: Studies in Congestive Heart Failure. VII. The Effect of Overwork on the Potassium Content of Skeletal Muscle. *J. Clin. Investigation* 9: 405, 1931.

Overwork of the muscles of one leg in dogs produced by stimulation of the sciatic nerve usually leads to a diminished content of potassium in these muscles as compared with those of the opposite unstimulated leg.

Calhoun, J. Alfred, Cullen, Glenn E., Clarke, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. VIII. The Effect of the Administration of Dibasic Potassium Phosphate on the Potassium Content of Certain Tissues. *J. Clin. Investigation* 9: 693, 1931.

The total solid and potassium content of skeletal muscle, of cardiac muscle from both ventricles and of liver and kidney have been determined in subjects dying without cardiac disease; individuals dying of congestive cardiac failure, who did not receive potassium salts, and patients dying of congestive cardiac failure who were given potassium dibasic phosphate during life. All the subjects with cardiac disease had had edema, although some of them had none at the time of death.

The organs of the "control" cases contained, as an average, more potassium in both the wet and dry tissues than was found in the subjects with cardiac disease.

Among the subjects with cardiac disease, the average content of tissue potassium was greater in the subjects who received the potassium salt than in those who did not. The difference was most striking in the skeletal muscle and least marked in the heart.

Eyster, J. A. E., and Meek, Walter J.: Studies on Venous Pressure. *Am. J. Physiol.* 95: 294, 1930.

Venous pressure in the dog under anesthesia tends to show relatively small and transitory changes under conditions which alter markedly the physical conditions existing in the cardiovascular system. There appear to be compensatory factors present tending to prevent excessive changes and to cause rapid restoration to a normal level.

There appears to be little if any direct relation between arterial pressure and the pressures in different parts of the venous system. Inverse changes occur as frequently as direct, and both may be present simultaneously if different parts of the venous system are considered.

In general the pressure is more stable and less subject to alteration in the peripheral veins than in the right auricle. There appears to be some factor or factors tending to reduce the extent of change arising at the heart as measured further out in the vascular system. Not infrequently inverse changes may occur in the periphery as compared with the auricular pressure change, but in all cases the result is transitory and rapid readjustment occurs.

These results tend to emphasize the fact that the vascular system particularly the venous part cannot be reduplicated physically by a simple hydraulic model. Many factors, some unknown and some only partially recognized, modify markedly the comparison to a more or less static system of channels. Two of these factors, the varying response of the heart to varying venous loads and the variable capacity of the vascular bed, would seem to be of essential importance.

Stewart, Harold J., and Moore, Norman S.: The Number of Formed Elements in the Urinary Sediment of Patients Suffering from Heart Disease, With Particular Reference to the State of Heart Failure. *Jour. Clin. Investig.* 9: 409, 1930.

The present study is concerned with the estimation of the number of formed elements in the urine of patients suffering from chronic heart disease, especially in the so-called arteriosclerotic type more particularly with reference to the state of heart failure of the congestive type.

The most consistent finding was increase in the number of casts, the average being 20 to 60 times greater than normal, depending on the severity of the disease. The number was smallest when failure of the congestive type had not occurred, somewhat greater when it had, though at the moment no signs were present and greater still when they were.

During heart failure and after recovery increased numbers of red and white blood cells occur almost so frequently they are within the normal range.

Moon, V. H., and Stewart, H. L.: Experimental Rheumatic Lesions in Dogs and in Rabbits. *Arch. Path.* 11: 190, 1931.

While conducting experiments on chronic focal infections with streptococci, results were obtained that are of interest because of their bearing on the pathogenesis of rheumatic fever. Young dogs and rabbits not subjected to sensitization or other previous treatment were inoculated with *Streptococcus viridans* from a case of bacterial endocarditis in man. The manifestations of disease which followed were very similar to the clinical features of acute rheumatic fever. The gross and microscopic lesions in these animals were identical with those that characterize rheumatic disease. The organism inoculated was recultivated from some of the lesions and was demonstrated microscopically in sections from others.

These results followed a combination of intravenous inoculation with implantation of chronic focus. The authors maintain that this mode of inoculation is not essential to production of the lesions. They believe the use of young animals and of freshly isolated cultures was of great importance in producing the lesions described. These results strengthened the evidence that streptococci of low virulence are the direct cause of rheumatic disease.

Gordon, Harry, and Perla, David: Subacute Bacterial Endarteritis of Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis. *Am. J. Dis. Child.* 41: 98, 1931.

An incidence is reported of subacute bacterial endarteritis of the pulmonary artery associated with a patent ductus arteriosus and a congenital pulmonary stenosis; none of the valves were involved. The relationship of congenital defect to bacterial inflammation is discussed. The group of cases analyzed suggests strongly the importance of mechanical stress.

Richards, Dickinson W., Riley, Constance B., and Hiscock, Mabelle: Congenital Heart Disease. Measurements of the Circulation. *Arch. Int. Med.* 47: 484, 1931.

Clinical, physiologic and pathologic studies have been made in a case of congenital malformation of the heart, the anatomic lesions of which were those forming the tetralogy of Fallot combined with a patent ductus arteriosus. The course of the circulation is described and illustrated by a chart.

From the point of view of experimental method this study has been of especial interest in that the technic employed is shown to have given fairly accurate results with at least one type of pathologic circulation.

Saphir, Otto: Endocardial Pockets. *Am. J. Path.* 6: 733, 1930.

In two cases of subacute bacterial endocarditis of the aortic and mitral valves with insufficiency of the aortic valve, endocardial pockets with openings toward the aorta were found on the interventricular septum of the left ventricle. The initial lesion which brought about the pocket formation was a circumscribed parietal endocarditis. The continuous regurgitation formed the pockets secondarily.

In one case of rheumatic endocarditis of the mitral valve with insufficiency of this valve, endocardial pockets were present in the left auricle. These pockets were open toward the mitral valve. They also were primarily inflammatory in origin and formed secondarily by the regurgitation after the insufficiency of the mitral valve had been established.

In two cases of syphilitic involvement of the aortic valve with insufficiency of this valve, endocardial pockets open toward the aorta were found. These pockets were caused primarily by the mechanical irritation of the regurgitating blood columns.

Two cases of syphilitic involvement of the aortic valve with insufficiency of this valve and marked stenosis of the *conus arteriosus sinister*, and one case of rheumatic endocarditis of the aortic valve with stenosis of its orifice, showed endocardial pockets on the interventricular surface of the left ventricle. These pockets were open toward the apex of the heart. They were brought about by the mechanical irritation of the systolic blood stream acting as a trauma upon the endocardium in the region of the stenosed portions.

From these observations it is concluded that diastolic endocardial pockets are evidence in favor of the view of actual regurgitation of blood volume.

The nomenclature of "diastolic pockets" referring to those open toward the aorta and "systolic pockets" referring to those open toward the apex (Krasso) is justified.

Endocardial pockets cannot be regarded as manifestations of functional adaptation.

Taussig, Helen B.: On the Boundaries of the Sino-Auricular Node and the Atrio-Ventricular Node in the Human Heart. *Bull. Johns Hopkins Hosp.* 48: 162, 1931.

Blocks of tissue from human hearts were sectioned and the cellular morphology of the S-A and A-V node were studied. It was possible to recognize the limits of these two nodes.

The study shows that in the human heart in certain places at the margin of the A-V node one can trace a gradual transition from the A-V nodal tissue to the auricular cardiac muscle. It was shown that the specialized tissue cells at the outer margin of the sino-auricular node are larger than those in the center of the node also there are purkinje cells extending from the S-A node into the outer wall of the superior vena cava. There are cells closely resembling specialized tissue cells extending from the S-A node into the folds of the auricular musculature. Extensive literature is appended.

Schmitz, Herbert W.: Urobilinuria in Children with Rheumatic Heart Disease. *Am. J. M. Sc.* 181: 392, 1931.

This study was concerned with the urinary urobilin estimations on children with rheumatic heart disease during different stages of the disease. Determinations were made on 57 ambulatory cases, 4 cases with recurrent rheumatic carditis without congestive failure and 10 cases of congestive heart failure.

Children with recurrent infection of the heart, but with no evidence of congestive failure may show normal values for the urobilin excretion in a twenty-four-hour period. High values for the urinary urobilin may be observed in children with congestive heart failure, but a high urobilinuria is not necessarily present in these cases, nor does a hyperurobilinuria in children with rheumatic heart disease always mean congestive failure. The urobilinuria does not bear a consistent relationship to the degree of congestive failure and, therefore, cannot be considered a reliable index of the functional efficiency of the heart. It is of no significant value in the diagnosis of the degree of damage, prognosis or the management of the cardiac child.

Bland, Edward F., Balboni, Gerardo M., and White, Paul D.: Enormous Increase of Heart Volume with Mitral Stenosis. *J. A. M. A.* 96: 840, 1931.

A young man with mitral disease under observation for nineteen years lived a relatively active life up to the time of his sudden death in spite of an extraordinary amount of cardiac enlargement and an extreme degree of auricular dilatation.

The volume of the filled heart was 4600 c.c., which is from six to seven times that of a normal sized heart and establishes a record for future comparison. In the case recorded cardiac hypertrophy was far less a factor than dilatation in causing the extreme enlargement; the weight was 850 grams, which has often been exceeded. The left auricle had a capacity of 1760 c.c., a measurement exceeded by only three other cases in the literature. The right auricle held 650 c.c. which appears to be a record capacity.

The authors found the literature to be notably deficient in measurements of heart volume. A determination that should be a helpful indication of the degree of responsibility of cardiac dilatation in the production of cardiac enlargement.

New England Heart Association

Sprague, Howard B.: Auscultation and Heart Sounds.

Reid, William D.: Heart Murmurs in the Practice of Medicine.

McCrudden, Francis H.: Heart Murmurs and Insurance.

Weiss, Soma: The Normal Arterial Blood Pressure and Its Measurement.

Palmer, Robert Sterling: Abnormal Blood Pressure.

O'Hare, James P.: Treatment of Hypertension.

New England J. Med. 204: 583, 1931.

These abstracts represent papers presented at the annual meeting of this association. In abstract form, they discuss the various subjects briefly. These subjects are of general interest and the material presented is clear and much to the point.

Book Reviews

ARTERIAL HYPERTENSION. By Edward J. Stieglitz, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago. New York, 1930, 180 pages, with illustrations, Paul B. Hoeber, Inc.

The purpose of Stieglitz' book is to give us "the logic of physiologic mechanism" of arterial hypertension so that it may be used at the bedside. He has boldly outlined a theory of the mode of production and maintenance of elevated blood pressures that has the advantage of the simplicity inherent in all unitarian doctrines. Two paragraphs quoted from pages 41 and 44 may possibly give the drift of his argument:

"A fundamental conception to be kept in mind, therefore, is that hypertension essentially results from vascular muscular hypertonia and that when the term 'vascular disease with hypertension' is used it signifies this hypertonia and its subsequent anatomic changes."

"The continuous spasticity therefore leads first to hypertrophy, then to fatigue and finally to hyperirritability, and of course to a further increase in the arterial muscular spasticity. Thus a vicious circle is set in operation. The continuation of the cycle of spasticity, fatigue, hyperirritability, more spasticity, fatigue, etc., is the second of the fundamental etiologic or physiologic phenomena and can well be called 'the perpetuating process of hypertension' in contrast to the 'initiating' process already discussed."

The subject has been presented with a great deal of enthusiasm and the book should appeal to all the lovers of progressive medical thought. The main contentions are, of course, based largely on theory, and the original will have to be studied if it is desired to obtain the spirit of the presentation. Stieglitz stresses the good effects of bismuth subnitrate and of bromides in the treatment of hypertensive states; he is the originator of the idea that the slow liberation of nitrites from bismuth subnitrate in the intestinal canal serves to keep the spastic arterioles in a relaxed state. There are some rather radical statements such as the idea that iodide therapy in arterial disease is grossly illogical and is actually contraindicated because the effect of iodine is one of destruction and weakening of the supporting scaffolding which is being placed about the tottering vascular walls; that the urinary specific gravity with renal decompensation is from 1.002 to 1.006; that

the renal tubules do not reabsorb sugar from glomerular urine but cause it to disappear by utilizing it and many others. Such ideas are teeming with interest and they should form starting points for new ways of thinking that may break the trail for advance in clinical medicine.

H. O. M.

The American Heart Journal

VOL. VI

JUNE, 1931

No. 5

Original Communications

THE CORONARY ARTERY IN HEALTH AND DISEASE*

JAMES B. HERRICK, M.D.
CHICAGO, ILL.

THE title of this paper is a misnomer. It is too pretentious. He would be bold indeed who would presume to present in a single lecture all the facts connected with the coronary artery, and the solution of its numerous problems that have immediate or remote contacts with moot and recondite questions of anatomy, pathology, physics, chemistry, physiology. And it would be rashness itself if the attempt were made by one whose training has been chiefly along clinical lines. For the sake of one's reputation also, it is wiser to keep silent regarding some of these topics. Chaucer in his translation of Boethius' *Consolations of Philosophy*—the idea is Boethius' really, and not Chaucer's—has this delicious bit: "This feynede philosophe . . . seyde at the laste right thus: 'understondest thou not that I am a philosophe?' That other man answerde again ful bytingly, and seyde: 'I hedde well understonden it, yif thou haddest holden thy tonge stille.'" There is a lesson here that I have tried to take to heart. Often in the writing of this paper—perhaps not often enough—it has kept me mute when I have been tempted to speak. The caption might better be: "Comments on the Coronary Artery and Its Diseases from the Clinical Point of View."

In the last thirty or thirty-five years there has been a revival of interest in, and a revision of our ideas of, the heart and its diseases. This is the period of the polygraph, the electrocardiograph, heart-block, circus movements, bacterial endocarditis, Aschoff bodies, quinidine.

In this re-study of the heart, the coronary artery naturally has had attention. But it is only in the last twenty years and particularly in the last decade that the interest in the normal and pathological anatomy, the physiology and diseases of this important vessel has become keen and widespread. In this paper the approach to the subject will be by way of clinical medicine. That was my avenue of approach about twenty

*The Harvey Lecture, read at the New York Academy of Medicine, March 19, 1931.

years ago when my attention was sharply attracted to the subject by a case of acute thrombosis of the coronary artery. It is chiefly by a consideration of the clinical and pathological features of acute occlusion of the artery that American physicians became interested in the subject and made so many noteworthy pioneer observations.

The acute or subacute type with frank symptoms is the one that is best known; it is the form that is generally meant when coronary occlusion or infarct of the myocardium is mentioned. In the United States it is regarded as not uncommon. Yet many writers, especially in Europe where a comparatively tardy interest has been manifested, still refer to it as rare. It is plain that what we look upon as acute infarction either is not so common in Europe as in this country or is classed as some other affection, perhaps angina pectoris. When one recalls one's own experience or talks with colleagues concerning theirs; when one reads the reports of cases by Levine, Conner and Holt, Willius, and Barnes, each with a series close to, or above, the hundred mark; when one learns that the Medical Department of one of the large life insurance companies in 1930 had 239 death claims in which the attending physicians returned diagnoses of coronary obstruction; when one considers the many cases of sudden death caused by acute thrombosis, cases that more often come to the attention of the coroner than of the practitioner; and when one includes also the often unrecognized mild and latent cases, one is convinced that the condition is not a rarity. We may add that coronary thrombosis is seen not alone in North America and Europe. Reports come from other continents. Last year Battro of Buenos Aires published an excellent monograph with clinical and experimental observations.

The question naturally arises whether the remarkable prevalence is due to an increasing frequency of coronary thrombosis or is merely due to the fact that the condition is better recognized today than formerly.

If we review the older literature; if we re-read Osler, Huchard or Mackenzie in the light of present-day knowledge, we see that not a few cases regarded as angina were evidently cases of infarction. And the splendid monographs of René Marie on infarct of the myocardium (1897) and of Sternberg on partial aneurysm of the heart (1914) are teeming with records, the clinical significance of which was overlooked because the vision of the writers as of the readers was focussed on the pathology. It is clear that this is no new disease.

It may seem incredible that such startlingly dramatic symptoms should so long escape the attention of physicians and pathologists. Yet strange, almost ludicrous, oversights are no novelty in medical history. Typhus and typhoid fevers were long confused. The development of a clear cut conception of appendicitis is well within the memory of many of us. For how long a time have undulant fever, encephalitis, tularemia and other supposedly rare diseases been given a wrong or meaningless

label? One of the explanations then, probably the chief explanation, for this apparent increase is a better understanding and more frequent recognition.

On the other hand, there is an impression, supported by several studies, that thrombosis in general is on the increase. While reference is chiefly to thrombosis in veins, it may be that the same causes, whatever they are, operate to multiply the instances of arterial thrombosis, especially in the coronary arteries.

The explanation offered by some that the development of thrombi is favored by the more frequent use of drugs intravenously does not seem attractive, at least in regard to arterial thrombi. I am certain that in only a very small proportion of my patients has there been previous intravenous therapy of any kind—arsphenamin, vaccines or what not. Nor do Singer's studies from the Leipzig clinic bear out this theory as to venous thrombosis.

Do modern conditions of living make for an increase? One is tempted to answer that this may be a contributing factor, at least if one believes that the strenuous life with its speed mania tends to cause hypertensive and arteriosclerotic states, of which general conditions the coronary lesion is often but a part. It is also true that today more people are reaching adult or senescent years when degenerative vascular changes come on. Therefore, there are more coronaries to be affected with the lesions that favor thrombosis.

Does infection play a leading part in producing thrombosis in the coronaries? We are told that recent infections may cause an acute arteritis or a former infection may perhaps sensitize the vessel wall. In either case, it is suggested, thrombosis may be favored. Are some of the cases we are encountering today of the crop that was sown by the influenza pandemic of 1918? Why is thrombosis rare in rheumatic hearts though rheumatic mural changes in the vessels are not unknown, perhaps not unusual? Why does syphilis spare the main coronary trunks? What about Warthin's idea that syphilis, while not an immediate cause of coronary thrombosis, is a secondary influence in predisposing to such thrombosis as well as in causing sudden death? What of thrombosis in the veins of the heart? Are the veins as carefully observed as they should be, by the pathologists? The relation of infection to coronary thrombus formation is still an open question. The problem needs further study.

The essential lesion seems to be a narrowing of the vessel due to disease of the arterial wall that is generally rough from calcification. Marie said that coronary thrombosis always is due to a disease of the artery. "It is never spontaneous." Yet other factors may enter: The sluggishness of the blood current; qualitative and quantitative physical and chemical changes in the blood; variations in its viscosity or its content of albumin; alterations in the number of platelets or their

fragility. Whether changes in food, in the air we breathe, especially in our large cities with their automobile and factory fumes, may have an influence, is a matter for surmise. So far, no definite facts along this line are known.

The question is sometimes asked, why are the coronary arteries oftener the seat of arteriosclerosis and thrombosis than other arteries in the body. In answer, it is said that circulatory conditions in the heart are unique. The ceaseless motion of the coronaries, their constant subjection to extreme active and passive stress and pressure, their unusual kinks and tortuosities may help to explain a striking development of sclerosis with consequent thrombosis. Yet it is not clear why an artery that is almost never quiet should so readily develop thrombi.

Moreover, are the coronaries oftener involved in thrombosis than other arteries of similar size? The startling phenomena that so commonly announce the formation of coronary thrombi, together with the serious effects that follow, make them stand out as star performers in the tragedy of vascular disease that is always on the boards. Do figures show that the vessels of the brain, spleen, kidney, pancreas are less often thrombotically closed than those of the heart?

Acute obstruction has bulked large in the consideration of coronary disease. The earlier drawn clinical picture with its severe enduring, substernal or epigastric pain, unprovoked by effort, its attendant shock, lowered blood pressure, disordered and weakened heart condition, dyspnea, fever, leucoeytosis, pericardial rub, embolic complications; with death in a few hours or days from ventricular fibrillation or rupture, or with partial or complete recovery after a slow convalescence, this still stands as our type.

One often hesitates on the basis of slight active and residual manifestations to diagnose a condition traditionally and in reality so formidable. We must, however, admit into the cadre of the acute and sub-acute cases many milder and atypical types in which supposedly cardinal symptoms may be lacking.

Without taking up the details of these atypical forms—they are discussed by various authors—it may not be amiss to make a brief reference to the painless cases. Acute coronary obstruction has so naturally and unconsciously been associated in our minds with angina pectoris in which pain is almost by definition a part of the symptom complex, that it is difficult to eliminate this feature from our clinical conception of the accident. Yet it is clearly established that painless acute obstruction occurs.

It has been suggested, that normally certain areas of the heart are not only less vital than others, indifferent or silent they have been called, but also less sensitive. At autopsy fresh infarcts are sometimes found associated with multiple areas of fibrosis that speak for previous obstruction of small branches, yet no pain has been noted, no pain even

announcing the recent infarction. There has evidently been a very gradual and progressive narrowing of the artery by sclerotic processes. The area irrigated by the artery has become relatively inactive, relatively anesthetized by destruction of vessels, nerves and functioning muscles, so that a painful response to the new obstruction is lacking. The final complete obstruction comes without a sudden shock, the element of surprise is lacking as the heart is in a sense prepared for the supreme insult. Abrupt heart failure with its dyspnea and other phenomena may be present, but pain may be lacking. These are the "substitution symptoms" in the hyposensitive described by Libman. As Obratzow and Strasesko expressed it, dyspnea may be the pain equivalent.

There is every clinical gradation in the severity of symptoms resulting from the sudden obstruction of the coronary artery, severe, moderately severe, mild. As results, early death, often sudden death, death after a cardiac breakdown, or a partial recovery with myocardial weakness as a hang-over, or perhaps a complete symptomatic restoration of function. These varying manifestations as well as the varying results must depend in large measure on the size, location, and functional importance of the arteries and muscular areas involved. They depend also on the degree to which compensatory enlargement of anastomosing vessels has prepared the heart for the attack.

Clinical features will depend to a large extent on the rapidity with which the obstruction is accomplished. The element of time is of great importance. American physicians and experimenters, heretofore largely concerned with the acute cases, must consider as well the group that may be called chronic. As this group is approached, it is realized that there is a difficult task ahead. To clear away the vagueness surrounding "chronic myocarditis," to differentiate at the bedside and in the dead-house between a process that in the stricter sense is inflammatory and one that is degenerative, the end-result of obstructive lesions, to learn what heart disturbances, especially what cases of heart failure, are due to slowly progressive coronary disease is a big undertaking. In the chronic cases there may be no dramatic announcement of the climax of the myocardial tragedy by sudden pain, dyspnea or drop in pressure. Often there is an insidious, gradual breakdown of the heart's efficiency with easily provoked dyspnea and palpitation together with irregularities and edema, due to the slow development of multiple areas of fibrosis that may by confluence become of considerable size. To quote Gallavardin's graphic and epigrammatic statement, the large infarcts are often infarcts that have enlarged, i.e., have grown to be large. "*Les grandes infarctus sont souvent des infarctus qui ont grandi.*" By this is not meant that all cases formerly called heart failure, chronic muscular insufficiency, dilatation of the heart, or break in compensation, are to be regarded as due solely to slowly developing obstruction in the

coronary arteries. Not at all. There are cases of heart failure due to rheumatic carditis in which with distinct valvular and myocardial lesions the arteries are comparatively healthy. Syphilis may be a cause even when the main arterial trunks are normal. The heart in obesity, in wasting diseases, in anemias; the worn-out heart associated with chronic nephritis, emphysema, scoliosis, goiter, may show no significant lesions in the coronaries. And there are cases in which intoxication and a vague something spoken of as fatigue are called in to explain the giving out of a heart that anatomically seems still fit to function. But the number of cases of heart failure due to progressive obstructive coronary lesions is very large. The coronary artery is a prolific disturber of health.

It is often difficult, at times impossible, to recognize these diseases, clinically. Morawitz laments the fact that the physician is so often chagrined because the autopsy discloses coronary conditions so different from what had been predicted. R. Kaufmann recently said that the pathologist looking at two hearts similarly involved in coronary sclerosis with secondary myocardial fibrosis, cannot tell in which case there has been a stormy clinical upset and in which case the symptoms have been mild and latent. We may well employ the term freakish, as does Ceeleu, to describe the entire arteriosclerotic process as well as its clinical manifestations.

Without elaborating this topic one may say in a general way that when a failing heart other than the heart of rheumatism or syphilis gives out more rapidly than is the rule, when cardiac asthma and acute pulmonary edema precede or accompany a drop in a previously high blood pressure, when gallop rhythm, feebler and more diffuse apex impulse with systolic mitral murmur appear and when in spite of rest and digitalis the heart fails to come back, there has perhaps, or probably, been an occlusion of a coronary artery or some of its branches with resulting infarction. This event—an epiphenomenon, Gallavardin aptly calls it—hurries the heart to its breakdown to which it was already slowly but surely progressing.

I wish to insert a comment concerning the diagnostic value of vagus pressure in suspected coronary disease. Wenckebach in 1914 in his book on the "Irregularities of the Heart" stated that a marked slowing of the heart produced by pressure over the carotids in the neck, especially the right carotid, was an evidence of myocardial weakness. Several writers, few in this country, have written on this subject. Opinions differ as to the worth of the test. My own impression is that there is something to it. Its almost uniform absence in those whose coronaries and heart muscle are presumably healthy—the young and cardioneurotic individuals; its increasing frequency in the senescent, aged and arteriosclerotic; the sometimes startling cessation of the heart beat in patients whose coronaries have recently been occluded and in

those whose hearts are inefficient, supposedly from myofibrosis, have made me feel that the test is of some value. One must agree, however, that Wenckebach is right in not assigning to it the virtues of an infallible sign; it may be lacking when one would expect it, it may be manifest at least to a moderate degree when one sees no reason for its presence. It may be added that the results of this simple pressure over the carotid are not alone confined to slowing of the heart's rate. There are, as was shown several years ago, in one of the most important contributions concerning the subject, being that of your presiding officer, Alfred Cohn, differences between the effects of stimulating the right and left vagus. The former has an influence that is especially chronotropic, the latter dromotropic. Other results shown chiefly through the electrocardiogram and of especial physiological interest, need not concern us here. The test needs further study at the bedside as well as in the laboratory. Even the rationale of its production is not yet agreed upon. Hering, it will be recalled, does not accept the direct vagal stimulation explanation. He regards it as a carotid sinus reflex.

In the study of coronary disease much use has been made of electrocardiography. Without attempting a comprehensive review of this topic, I wish to call attention to a few facts that seem to warrant consideration.

Taking up first the electrocardiogram in acute obstruction; when local necrosis of the myocardium has been brought about acutely by direct experimental destructive injury of tissue, or in an indirect manner by cutting off the coronary circulation as by ligation; or when such myomalacic lesion in man is the result of coronary thrombosis or the rare surgical ligation of the artery for stab wounds, fairly characteristic electrocardiographic findings have been noted. One feature needs repetition lest it be forgotten. It is that the electrocardiogram in these cases of acute myocardial destruction is not fixed, that for a long time it undergoes change. This was shown experimentally even as far back as 1910 when Eppinger and Rothberger injected silver nitrate into given areas of the heart muscle. It was observed by Samajloff in 1911. Fred Smith, in his classic experiments, showed that after ligation of the left coronary artery of dogs, especially the descending branch, fairly uniform changes were noted in the electrocardiogram, a prompt increase in the height of the T-wave, with a subsequent early drop to a negative state and then a slow return toward, or to, its old positive position. Smith's work on the coronaries of dogs has been quite generally confirmed as has the transference of most of these results to man. There are numerous clinical observations confirming this feature of the experiments. The very title of Parkinson and Bedford's article, "Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis)," declares that the picture is not fixed. But not all writers, and by no means all practitioners, take account of the

fact that the electrocardiogram, registering regressive and reparative processes should and does show variations from day to day or month to month. The physician who gets his tracing right after the accident sees the prominent T-wave with the high take-off from R-wave. The one whose tracing is made a week or several weeks later stresses the altered, often inverted, T-wave or the Pardee coronary wave or some peculiarity of QRS, perhaps its broadening or slurring. Each observer is apt to generalize and declare that such and such a picture is characteristic—the characteristic it is sometimes expressed—of acute coronary obstruction. Conflicting and confusing statements might be avoided if the time relations were better realized, if it were recognized that the pathological process is for many weeks at least, one of change, which change is reflected in an electrocardiogram that for a long time is not stable.

A second point: Not all the electrocardiographic abnormalities noted in a given case are necessarily due to some recent event heralded by symptoms suggestive of acute coronary or myocardial accident. The *post hoc ergo propter hoc* argument is as fallacious here as in therapeutics. Earlier gradual narrowing and blocking of diseased vessels may have resulted in myocardial fibrosis, the process being as varied and as scattered as to time as the lesions are as to size and location. The electrocardiogram, translating the progressive myocardial changes, may be evolutive as Clere has called it, complexes broaden and flatten, extrasystoles appear or auricular fibrillation with paroxysms of tachycardia and perhaps final “anarchy.” Some of the abnormal, bizarre tracings then, may be due to old lesions long antedating the present symptoms, or may be associated with cardiac hypertrophy attendant on hypertension. Carter in the discussion last year in the Association of American Physicians very justly emphasized these points.

But aside from these considerations there is need for still further study of electrocardiography in acute and chronic cases.

There is a consensus of opinion that changes in the T-wave are the ones most frequently seen in a recent or old coronary obstruction; Nathanson says in 88 per cent of cases. Inversions in Leads I or II, the “high take-off,” Pardee’s coronary wave are met with so often that they cannot be regarded as meaningless or accidental. Other changes noted in acute cases, extrasystoles, atrioventricular block, paroxysms of tachycardia of various types, even short paroxysms of ventricular tachycardia, are not so generally regarded as pathognomonic.

But the significance of many alterations seen long after an acute occlusion or when the occlusion has been insidious or slow is not always clear—broad P-waves, a prolonged P-R interval, a QRS complex slightly slurred or perhaps distorted almost beyond recognition by exaggerated notching, broadening and displacement below the line. Even though symptomatically a heart may seem functionally normal, if it records such abnormal electrocardiograms there is reason to believe there

are organic changes that cause interference, not necessarily serious, with conductivity and presumably with other functions as well. But knowledge sufficiently precise to enable one to state definitely what is the location, size or age of the lesion is often lacking. There is no agreement as to the meaning of arborization block. That it has an important significance seems certain. F. N. Wilson and his associates, the Oppenheimers, and others are massing evidence to show that what has long passed for right bundle-branch block is really left branch block and vice versa. Barnes and Whitten on the basis of anatomical, clinical and post-mortem studies, declare that obstruction of the right coronary is more common than generally supposed; that infarcts in the basal posterior portions of the left ventricle and of the septum and at times even of the apex may be produced by such obstruction. They believe that by a study of the electrocardiogram, grouping the tracings after the classification of Parkinson and Bedford, one may with some approach to accuracy know whether the obstructing clot is in the right or left coronary. Their suggestive work should be confirmed. They and others raise the important question as to how far human electrocardiograms may be compared with those obtained experimentally in the dog, for there are anatomical differences. Some of the posterior wall of the left ventricle, and parts of the septum that in the dog are generally nourished by the left coronary are cared for in man by the right. In this connection the recent work of Moore, Campbell, Gross, and Whitten is important.

What of a lowering of the various peaks, the so-called low voltage tracing? Does this mean merely a general weakening of the myocardium? Reappearance of higher voltage tracings after rest would seem to speak for such an interpretation in some instances. Or has the low voltage curve a more restricted significance? H. J. Stewart asks whether it may not mean a shutting off of the left circumflex artery as suggested by Fred Smith's experimental work as well as by a few clinical cases with autopsy control that have been reported. What of an exaggerated Q-wave in Lead III? It is more and more persistently, and it would appear justifiably, clamoring for admission into the select company of "high take-offs," inverted T's, and convex RT's that claim title to the coronary-crowned-peerage because they came in with William of Holland—William Einthoven—when he invaded and conquered the realm of cardiology. There is food for thought in Craib's conclusion that "the alteration in the electrocardiogram that results from local myocardial infarction depends upon the normal contribution of the region in question. . . . When 'silent areas' are infarcted the electrocardiogram is unaltered provided the infarction is not accompanied by gross dilatation or conspicuously diminished output per beat."

It is evident that there is need for further investigation of electrocardiography as related to coronary disease. Much as it goes against

the grain to admit our poverty of knowledge on this point, one must agree with Gilbert and Ritchie when, as the conclusion of their most critical study and summary of electrocardiography in myocardial infarctions and fibrosis, they say: "The evidence available at the present time does not lend support to the view that the form of the electrocardiographic distortion can be regarded as a definite localization of the infarct." Reports based on the study of large series of cases may carry conviction by the sheer weight of numbers, but critical reports of carefully worked out single cases, such as that of H. J. Stewart two years ago, also deserve commendation; the conclusions may be as convincing as those drawn from the larger series.

There is especial need of a study of the electrocardiogram in cases of coronary sclerosis of a chronic character, cases of disseminated myocardial fibrosis, of angina pectoris, of chronic myocarditis *sensu strictiori* such as may have resulted from rheumatic, syphilitic or other infectious processes. Besides, the transitory deviations from the normal electrocardiogram seen in acute infections as rheumatism, diphtheria and influenza, in uremia, in digitalization, etc., need further investigation.

It is important that clinical reports should describe more accurately the location of pain, its radiation, its deviation, skin tenderness; location of pericardial friction; degree of cyanosis, pulmonary and hepatic congestion; height of temperature; number of leucocytes; change in blood pressure. There are reasons why pain radiates to the epigastrium in one case, to the right arm in another, to the left arm in a third; why in one case there is a temperature of 102 degrees, in another that seems to be equally severe no fever at all; but the reasons are as yet obscure. By such careful bedside observation together with electrocardiograms taken at short intervals, and when possible with post-mortem examinations that take account of minute anatomical changes, much can be learned as to the nature and localization of these coronary lesions. New light may be shed on the physiology and pathology of the heart that may have rich application in practice. Gilbert and Ritchie state that up to 1930 there are only 148 case reports with sufficient detail to permit of satisfactory analysis. In only forty-four of these cases are post-mortem records available. I have elsewhere said, some cardiac Beaumont may yet find his Alexis St. Martin so that clinical, including electrocardiographic, data, may be based on observations made on man with conditions largely under experimental control.

It is desirable that our knowledge should be clarified and that as soon as possible. The electrocardiograph is more and more used in hospitals and in private practice. But it is here and there falling into disrepute. We often see the tracing interpreted by physicians of no special training, even by technicians who are not physicians at all. The assurance with which some of these pathological and topographical diagnoses are made is rather startling to one who is at all familiar with the surprises

of the dead-house. Minute, almost microscopic shurrings, slightest variations from the classic electrocardiogram are confidently declared to indicate some particular coronary or myocardial lesion, at times with a prognostic warning that all too often upsets the mental equilibrium of the practitioner, still more that of the patient. And these cocksure interpretations, as shown by subsequent events, are often wrong. All this may ultimately lead to a distrust of the electrocardiograph as an instrument that is even approximately precise. Such distrust is already manifest. "There was no negative T-wave, no coronary wave yet an infarct was found," or "a negative T was present and a broad QRS and yet no lesion was discovered, etc. What can we believe?" Some of the hospital and commercial laboratories recognizing this lack of definite knowledge, have become very wary and shrewd, perhaps we should say wise. They send in diagnoses of "myocardial damage." Possibly what is lost in definiteness of diagnosis is made up in a closer approximation to truth. Of course, the electrocardiograph is not at fault. It is our knowledge that is faulty.

When I began this paper I fully intended to discuss—I will not say settle—the question of the origin and nature of pain in angina pectoris. I have given up this plan. After reading many articles I found that my own notions, none too clear to start with, were still very nebulous, even more nebulous. I feared my presentation of the subject would not be convincing, for it is difficult to convert another to views that one is not certain about oneself. Besides, while there are many excellent discussions of the subject, many are but specious pleadings for the writer's pet theories, exercises in dialectic with little or no scientific proof. At times in reading the fine-spun academic and wordy arguments, one is reminded of the momentous question as to the proper way to open the egg and the heated controversy that arose therefrom between the Big-Endians and the Little-Endians, for details of which one may consult the immortal Lemuel Gulliver. Much of the recent discussion centers about experimental and surgical investigation concerned with the cervical sympathetic nerves and ganglia. As someone has said this work is based on an anatomy that is not precise, and a physiology that is poorly understood. While thus embarrassed by my own ignorance and by the bewildering conflict of views contained in the staggering mass of literature, I ran across several frank statements that comforted me and strengthened me in my decision to omit this feature. This by Wiggers: "An intelligent discussion of cardiac pain is not at present possible, for ideas as to the ultimate mechanisms producing pain remain wholly speculative." And one by Clere who, referring to the origin of angina pectoris as still a mystery, says that in the future as in the past, pages will be devoted to this enigma, and as another has stated, the course already pursued is short compared to that which must be followed before the goal is reached. And a third from Italy: "Angina pectoris

is an illness syndrome. Its pathogenesis is obscure; the etiological facts are uncertain and incomplete; the data of anatomical pathology, experimental physiology and physiopathology are insecure and bristling with inexplicable contradictions." If such are the views of a scientist unusually well informed as to cardiovascular physiology, and of physicians well read and with rich laboratory and clinical experience, why should I add to the bulk of this fruitless phraseology? Lapsing into the vernacular, I pass.

I cannot, however, resist the temptation to say a word as to the bearing of acute occlusion on the theories of angina pectoris. A clinician must have some notions on this point, speculative if not conclusive.

At the outset it may be said that in subscribing to the coronary theory of angina one need not deny that a diseased aorta may cause pain, a pain that at times is like that of coronary angina but that often lacks the earmarks of the typical form.

The two theories that have prevailed for two or more decades are the aortic and the coronary. Allbutt and after him, Wennekebach, Rudolf Schmidt, Vaquez, and many others have contended that the pain is due to a stretching of the diseased wall of the aorta. "Entzündung und Dehnung" is the explanation of Schmidt. "For me," declared Allbutt, "the coronary hypotheses are dead and buried." Many physicians, however, still cling to, and increasing numbers of them are becoming adherents of, the coronary artery theory, the theory that with various modifications has been the prevailing one since the time of Parry and Jenner.

Experience with cases of acute thrombosis of the coronary artery seems to strengthen the view that the paroxysm of angina of effort has its origin in a perversion of function of the coronary artery or the muscle supplied by that artery, or of both.

There can be no denial that the sudden closure of a coronary artery or one of its larger branches is often attended by pain that may resemble in every particular that of angina pectoris. Patients who have had previous anginal attacks on walking often speak of it as of the same kind only more severe, more persistent, more prostrating. It is unreasonable to assume that the pain preceding the occlusion has had its seat in the aorta while the similar though severer pain clearly has its origin in the obstructive lesion in the coronary artery. To contend that in the latter case the pain is really of aortic character because the pathway of transmission of the stimuli to the brain is by way of nerves that pass through the aortic adventitia on their way to the sympathetic trunks and the cord, seems illogical. One might as well argue that if the little finger is pinched in the door the pain has its origin in the ulnar nerve in the cubital fossa or in the brachial plexus because the ulnar nerve passes these points on its way to the cord and brain. The origin of the pain

is clearly in the crushed finger in the one case, in the coronary artery or the damaged muscle in the other.

Wenckebach lays stress on the fact that previous anginal pain generally ceases after an extensive infarction. This, he says, speaks for a resulting weakness of the ventricular wall, and a lessened pressure on the aortic wall. In reply one may say that there is no uniform result in regard to pain of an anginal character that follows a thrombotic accident. By no means do all cases of even extensive infarction lose their anginal pain. The status anginosus may continue for hours or days though muscular power is weak and blood pressure low. Not all patients who do lose the pain show lowered blood pressure or ventricular weakness. Furthermore, many patients have their effort angina ushered in by a stormy bout clearly due to obstruction of a coronary artery. May it not be that in some instances anginal pain ceases after the thrombotic occlusion because the artery with its nerves, and the affected patch of myocardium are in effect dead, functionless, incapable of responding to the stimulus of effort that formerly induced pain? May it not be that the fibrous patch has lost nearly all its specific functions like conductivity and contractility and is relatively painless? It may retain little except the rather characterless function of holding, i.e., not breaking. The very fact that when the vessels and the muscle cease to act there is no pain-response on effort speaks strongly for a direct connection between such artery or muscle or both and the pain of angina. When an attack of coronary thrombosis initiates anginal symptoms, may it not be that the artery is not completely shut off, or that some smaller branches are left partially occluded, capable on effort of inducing the condition—let us assume relative myocardial ischemia, anoxemia if you prefer, perhaps associated with spasm—that causes pain? The close association of the symptoms of these two conditions, obstruction in a coronary and pain, is something more than accidental. For the purpose of this argument it is immaterial whether the pain begins or ceases with the coronary occlusion. Either phenomenon is clearly associated with a suddenly developed anatomical change in the coronary artery and not in the aorta.

Take a case like this: A man of forty-seven years, supposedly in good health, is awakened at six in the morning in June, 1930, by a severe substernal pain radiating to both arms, a pain lasting in spite of morphin, for nine hours. He recovers from this attack and goes about his work, feeling quite well until November. Then distress in the sternal region on walking, with pains going to the arms, leads his doctor to diagnose angina, and to put him to bed. Again he improves but about the last of December as he resumes his activity, typical effort angina appears. Walking two blocks, especially in the cold, or after a heavy meal brings on the pain and causes him to stop. The physical examination reveals little that is abnormal. The electrocardiogram,

however, shows in Leads II and III inverted T-waves with the coronary wave of Pardee and some slurring of QRS. Interpreting these facts, there was an acute infarction in June, 1930, with recovery. In November a possible second infarction with less stormy symptoms, then typical angina of effort. Can one reasonably dissociate these phenomena and say that the pain in the first instance was coronary, in the second aortic? Clearly the burden of proof is on him who denies the coronary origin for both pains. This is but clinical evidence, but I see no other reasonable way to interpret the phenomena than on the basis of disturbance in the coronary artery.

There are many other arguments that support the coronary theory against the aortic. I wish to refer briefly to a few of these that have made a special appeal to me.

1. The contention that post-mortem examination generally bears out the aortic theory is not well founded. Not the least valuable part of Hans Kohn's comprehensive survey is his painstaking historical review of original records. He finds that many of the older observers—and some of the later ones are also negligent—really did not examine the coronary arteries or examined them carelessly. The overwhelming number of positive coronary cases would be still further increased if these vessels were examined more thoroughly, not the main trunks alone but smaller branches as well. It is so much easier to find lesions in the large, easily examined aorta than in the smaller coronary! Absence of detectable coronary lesion does not exclude spasm. Presence of diseased coronaries without angina is not conclusive proof of the correctness of the aortic theory. Kohn well says that we must not forget that the anatomical lesion is not the disease, rather the resulting disturbance of function and the reactive changes in the organism.

2. That angina is infrequently found with auricular fibrillation may be true. Auricular fibrillation is most commonly seen in rheumatic hearts, especially with mitral stenosis. But this is exactly where coronary obstructive lesions are rare, viz., in rheumatism.

As a corollary to this argument note the unusual case seen by Coombs and Perry. A child of fourteen with acute rheumatic carditis had angina pectoris, the only instance Coombs had come across in an unusually rich experience with rheumatic children. Autopsy showed marked narrowing of the coronary through acute rheumatic changes in the wall of the artery.

3. There are many hearts of "chronic myocarditis" whose cells are damaged by infections or toxic processes, e.g., rheumatism, typhoid fever, diphtheria, thyroid toxicosis. Such hearts may give out suddenly or gradually, but only rarely is pain a striking symptom. Only rarely do we find obstructing coronary lesions.

4. With syphilis angina is rare except in cases in which the coronary mouths are narrowed by the aortic process.

5. Nitrites and theobromine compounds dilate the coronaries. They often afford relief in angina of effort. It may be assumed that they relax a spasm or dilate the vessel so that the relative ischemia of the heart muscle is relieved.

6. Levine and others have by the injection of epinephrine provoked painful seizures in patients subject to angina. In younger individuals with supposedly normal coronary arteries no such pain was noted. The explanation offered that the increased work demanded of the myocardium by the rise in blood pressure cannot be met if there are obstructing coronary lesions, seems satisfactory.

7. Hypoglycemia induced by insulin has caused anginal distress. An area of heart muscle already poorly nourished because of arterial narrowing has its nutrition still further cut off by the reduced sugar content of the small amount of impoverished blood.

8. Similarly in severe anemia; blood of poor quality may be insufficient to meet the needs during effort—oxygen needs let us say—of some area in the heart muscle when the quantity of blood is lessened by a partly obstructed coronary; pain may result. In this instance as in hypoglycemia the threshold for pain is lowered by the circulatory insufficiency of the damaged coronary. If the amount of sugar or the amount of oxygen is increased, pain may disappear.

9. In hyperthyroidism whether induced by an inactive gland, or by feeding thyroxine in myxedema, anginal pain may appear. The heart muscle poorly supplied with blood by a damaged artery cannot meet the requirements of increased metabolism. If the metabolic rate be reduced, the angina may disappear.

In the last three instances (7, 8, 9) it is seen that the heart's ability to respond normally and painlessly to an increase in work demanded by exertion, heightened metabolism, greater peripheral resistance, etc., depends as well on the quality as on the quantity of blood that may get through the coronary artery. Means, in an article that has just come to hand, compresses much of this and similar argument into the epigrammatic statement that "the symptom angina pectoris is evidence of relative insufficiency of coronary flow."

10. In patients with angina electrocardiographic changes are frequently seen. As Grotel well remarks, these changes are by no means to be regarded as specific. Yet they are often due to muscular degeneration, the result of coronary disease. This degeneration by its close association with the anginal syndrome surely suggests a more intimate relation to the vessels of the heart proper than to the aorta.

Especially significant are the electrocardiograms taken during attacks of angina. Transitory variations in the ventricular complexes would seem to mean transitory changes in the heart muscle—perhaps coronary spasm and ischemia. Parkinson and Bedford exhibit tracings that resemble those seen at the beginning of coronary infarction. Feil and

Siegel, Bousfield, Willius, Wood and Wolferth and others report altered electrocardiograms during attacks.

11. In a small number of cases vasomotor phenomena, e.g., Raynaud's fingers, have been associated in a suggestive way with angina. Coincident coronary spasm seems far more likely to explain this combination than any change in the aorta.

12. While there is no unanimity of opinion as to the results of experimental work on animals, there are investigations, such as those of Sutton of Chicago, that seem to show that temporary occlusion of a coronary, a condition comparable to spasm, induces pain.

As I go back over this lecture to see what it is all about—is not that the way most papers are written?—I find that there is a thread of thought, rather slender at times I admit, that binds together the seemingly disconnected pieces out of which this paper has been constructed. The motif seems to be not so much to declare what we know concerning the coronary artery and its diseases as to point out certain gaps in our knowledge, certain problems that still await solution: the cause of arteriosclerosis and thrombosis; the pathology of chronic obstruction and its disease manifestations; the pitfalls of electrocardiography; the mystery of cardiac and especially anginal pain. At this point I might well, after the manner of the preacher or the commencement orator of other days, utter the perorational exhortation: "Let us then" realize that there is need for cooperation between the practitioner of medicine; the pathologist, the experimental physiologist and pharmacologist, the student of electrocardiography. Intensive, concerted investigation will surely bring forth rich results.

I am conscious also of harboring the thought and hinting at it in a tentative way that we should view the coronary lesions here described and the diseases caused thereby as one process rather than as several. Whether this process is acute or chronic, whether the lesions are slight or extreme, whether the results are mild or serious, there is a common unifying element—obstruction to the coronary flow. Klotz and Lloyd state the order of pathological events as endarteritis, atheroma, calcification, stenosis, thrombosis. We might add infarction and myofibrosis. If now we mix clinical and pathological features, we may slip into this list as we approach and leave thrombosis such terms as chronic or acute heart failure, ventricular fibrillation, sudden death.* And—I quote Le Count—"Somewhere between sudden occlusion and its results, and such slowly developing obstruction that few or no symptoms develop, lie the lesions responsible for angina pectoris."

In closing, much of our knowledge concerning the coronary artery and much of the present day interest can be traced to the impetus given

*Coronary obstruction and ventricular fibrillation seem to offer the most rational explanation of the sudden death in angina. There may be instances in which obstruction is complete without a thrombus. Usually, however, there is a thrombus. The clot, however, may easily be overlooked if death occurs before the more strikingly visible changes of infarction have taken place.

to the study of this subject by the observations of clinicians. Perhaps Scott is right when he says: "Medical history of the future doubtless will record as one of the important contributions to clinical medicine of the past twenty years the general recognition of coronary thrombosis." If this is so, it is one more argument to support the position so admirably outlined by Rufus Cole the other day before this body, that medicine—practical medicine—can now without apology hold up its head among the company of the physical and biological sciences that, while perhaps more exact, are not inspired by ideals more lofty, methods more honest or results more far reaching and beneficial. Without Dr. Cole's address, I should not have ventured to appear before you to present a paper so largely clinical. With his address I plucked up enough courage to accept the very kind invitation to deliver this Harvey Lecture, an invitation that I regard as a high honor and for which I thank you most sincerely.

REFERENCES

1. Barnes and Whitten: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.
2. Benson, Robert L.: The Present Status of Coronary Arterial Disease, *Arch. Path. and Lab. Med.* 2: 876, 1926. (Has full bibliography.)
3. Bousfield: *Lancet* 28: 484, 1918.
4. Campbell, John A.: Stereoscopic Radiography of the Coronary System, *Quart. J. Med.* 22: 247, 1928-29.
5. Ceelen, W.: Ueber den jetzigen Stand der Lehre von den Myokarderkrankungen, *Deutsch. med. Wchnschr.* 55: 569, 1929.
6. Clarke and Smith, F. J.: Electrocardiogram in Coronary Thrombosis, *J. Lab. & Clin. Med.* 11: 1071, 1926.
7. Clerc, A.: Angine de Poitrine et Theorie Coronarienne, *Presse méd.* 35: 593, 1927.
8. Clerc, A.: Anomalies Electrocardiographiques au Cours de l'Obliteration Coronarienne, *Presse Méd.* 35: 499, 1927.
9. Clerc, Bascourret et Levy: Valeur de l'Electrocardiographie, etc., *Ann. de Méd.* 21: 201, 1927.
10. Cohn, Alfred E.: On the Differences in the Effects of Stimulation of the Two Vagus Nerves on Rate and Conduction of the Dog's Heart, *J. Exper. Med.* 16: 732, 1912.
11. Cole, Rufus: Progress of Medicine During the Past Twenty-five Years as Exemplified by the Harvey Society Lectures, *Science* 71: 617, 1930.
12. Conner, L. A., and Holt, E.: Subsequent Course and Prognosis of Coronary Thrombosis, *AM. HEART J.* 5: 705, 1930.
13. Coombs, Carey: Observations on the Aetiological Correspondence Between Anginal Pain and Cardiac Infarction, *Quart. J. Med.* 23: 233, 1930.
14. Coombs and Hadfield: Ischaemic Necrosis of the Cardiac Wall, *Lancet* 1: 14, 1926.
15. Cottrell and Wood: The Effect of Epinephrin in Angina Pectoris With Report of a Case, *Am. J. M. Sc.* 181: 36, 1931.
16. Craib, W. H.: The Electrocardiogram, London, 1930, His Majesty's Stationery Office.
17. Danielopolu: Ueber den Mechanismus der Beendigung des Anfalles von Angina Pectoris, *Klin. Wchnschr.* 8: 596, 1929.
18. East, Bain Clary: Cardiac Infarction Without Pain, *Lancet* 2: 60, 1928.
19. Eppinger and Rothberger: *Wien. klin. Wchnschr.* 22: 1091, 1909.
20. Feil and Siegel: Electrocardiographic Changes During Attacks of Angina Pectoris, *Am. J. M. Sc.* 175: 255, 1928.
21. Gallavardin and Gravier: Formes Cliniques de l'Infarctus du Myocarde, *Ann. de Méd.* 20: 161, 1926.
22. Gallavardin and Rougier: Accès d'angine de poitrine avec hypotension artérielle. Extrême et accidents nerveux syncopaux et épileptiformes, *Paris méd.* 2: 15, 1928.

23. Goldenberg and Rothberger: Ueber den Krampf der Coronargefäße, Wien. klin. Wchnschr. 43: 1197, 1930.
24. Grotel, D.: Elektrokardiographische Beobachtungen bei Koronararterienthrombose und Angina Pectoris, Deutsch. Arch. f. klin. Med. 169: 44, 1930.
25. Hamburger and Priest: Experimental Coronary Embolism, Am. J. M. Sc. 171: 168, 1926.
26. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefäße, Dresden and Leipzig, 1927, Th. Steinkopff.
27. Herrick, James B.: Clinical Features of Sudden Occlusion of the Coronary Arteries, J. A. M. A. 59: 2015, 1912.
28. Herrick, James B.: Thrombosis of the Coronary Arteries, J. A. M. A. 72: 387, 1919.
29. Herrick, James B.: On the Combination of Angina Pectoris and Severe Anemia, AM. HEART J. 2: 351, 1927.
30. Herrick, James B.: Some Unsolved Problems Connected With Acute Obstruction of the Coronary Artery, AM. HEART J. 4: 633, 1929.
31. Herrick, James B., and Nuzum, Frank R.: Angina Pectoris, J. A. M. A. 70: 67, 1918.
32. Herrick, James B., and Smith, Fred M.: Clinical Observations on Block of the Branches of the Auriculo-ventricular Bundle, Am. J. M. Sc. 164: 469, 1922.
33. Hurxthal, L. M.: The Appearance Time of T-Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion, Arch. Int. Med. 46: 657, 1930.
34. Juster and Pardee: Abnormal Electrocardiograms in Patients With Syphilitic Aortitis, AM. HEART J. 6: 162, 1930.
35. Kaufmann, R.: Ueber Probleme des Koronararterien-Kreislaufes, Wien. klin. Wchnschr. 39: 437, 1926.
36. Keefer and Resnik: Angina Pectoris; Syndrome Caused by Anoxemia of Myocardium, Arch. Int. Med. 41: 769, 1928.
37. Klotz and Lloyd: Sclerosis and Occlusion of the Coronary Arteries, Canad. Med. Assn. J. 23: 359, 1930.
38. Kohn, Hans: Angina Pectoris, Med. Klin. 22: 983, 1926; also Ergebnisse d. ges. Med. Band 9.
39. LeCount, E. R.: Pathology of Angina Pectoris, J. A. M. A. 70: 974, 1918.
40. Levine and Brown: Coronary Thrombosis, Medicine 8: 245, 1929.
41. Levine, Ernestene and Jacobson: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, Arch. Int. Med. 45: 191, 1930.
42. Marie, René: L'Infaretus du Myocarde et Les Consequences, Paris, 1897, Carré et Naud.
43. Means, J. H.: Certain Aspects of the Pathogenesis of Angina Pectoris, Can. Med. Assn. J. 24: 193, 1931.
44. Middleton and Otway: Insulin Shock and the Myocardium, Am. J. M. Sc. 181: 39, 1931.
45. Moore: The Coronary Arteries of the Dog, AM. HEART J. 5: 743, 1930.
46. Morawitz: Pathogenese, Diagnose und Therapie der Angina Pectoris, Deutsch. med. Wchnschr. 55: 1993, 1929.
47. Morawitz and Hochrein: Zur Diagnose und Behandlung der Koronarsklerose, Münch. med. Wchnschr. 75: 17, 1928.
48. Nathanson: The Electrocardiogram in Coronary Disease, AM. HEART J. 5: 257, 1930.
49. Obratzow and Strashesko: Zur Kenntniss der Thrombose der Koronararterien des Herzens. Ztschr. f. Klin. Med. 71: 116, 1910.
50. Oppenheimer, B. S., and Oppenheimer, Enid Tribe: The Site of the Cardiac Lesion in Ten Cases of Intraventricular Block Including Bundle-Branch Block and Arborization Block, Trans. Assn. Am. Physicians 45: 427, 1930.
51. Pardee, H.: The Significance of an Electrocardiogram With a Large Q in Lead III, Arch. Int. Med. 46: 470, 1930.
52. Parkinson and Bedford: Electrocardiographic Changes During Brief Attacks of Angina Pectoris, Lancet 220: 15, 1931.
53. Perry, C. B.: The Main Branches of the Coronary Arteries in Acute Rheumatic Carditis, Quart. J. Med. 23: 241, 1930.
54. Pontano: La Riforma Medica 42: 1062, 1926.
55. Ryle, John A.: John Hunter's Cardiac Infaret, Lancet 2: 332, 1928.
56. Samajloff, A.: Pflüger's Arch. f. d. ges. Physiol. 135: 417, 1910.
57. Schmidt, R.: Zur Kenntniss der Aortalgie (Angina Pectoris) und Ueber das Symptom des Anginosen linkseitigen Plexusdruckschmerz, Med. Klin. 18: 6, 1922.

58. Scott, R. W.: Coronary Thrombosis, *Canadian Med. Assn. J.* 23: 366, 1930.
59. Scott, Feil, Katz and Moore: Electrocardiographic Studies in Experimental Myocardial Ischemia, *Trans. Assn. Am. Physicians*, May, 1930.
60. Smith, Fred M.: Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch. Int. Med.* 32: 497, 1923.
61. Smith, Fred M.: The Ligation of Coronary Arteries With Electrocardiographic Studies, *Arch. Int. Med.* 22: 8, 1918.
62. Sternberg, M.: Das Chronische Partielle Herzaneurysma, Leipzig und Wien, 1914, F. Deuticke.
63. Stewart, H. J.: The Relation of Clinical, Including Electrocardiographic, Phenomena to Occlusion of the Coronary Arteries, *AM. HEART J.* 4: 393, 1929.
64. Sutton and Luth: Pain, *Arch. Int. Med.* 45: 827, 1930.
65. Travers, Paul: Ueber das Verhalten des Blutzuckers bei Herzkranken unter besonderer Berücksichtigung der therapeutischen Anwendung von intravenöser Traubenzucker-infusionen, *Deutsh. Arch. f. kl. Med.* 137: 284, 1921.
66. Turner, K. B.: Insulin Shock as the Cause of Cardiac Pain, *AM. HEART J.* 5: 671, 1930.
67. Warthin, A. S.: The Rôle of Syphilis in the Etiology of Angina Pectoris, Coronary Arteriosclerosis and Thrombosis, and of Sudden Cardiac Death, *Trans. Assn. Am. Physicians* 45: 123, 1930.
68. Wenckebach, K. F.: Angina Pectoris and the Possibilities of Its Surgical Relief, *Brit. Med. J.* 1: 809, 1924.
69. Whitten, Merritt B.: The Relation of the Distribution and Structure of the Coronary Arteries to Myocardial Infarction, *Arch. Int. Med.* 45: 383, 1930.
70. Wiggers, C. J.: Physiologic Meaning of Common Clinical Signs and Symptoms in Cardiovascular Disease, *J. A. M. A.* 96: 603, 1931.
71. Willius, F. A.: Angina Pectoris; an Electrocardiographic Study, *Arch. Int. Med.* 27: 192, 1921.
72. Wood, Francis C., and Wolferth, Charles C.: Angina Pectoris—The Clinical and the Electrocardiographic Phenomena of the Attack, etc., *Arch. Int. Med.* 47: 339, 1931.

SERIAL ELECTROCARDIOGRAPHIC STUDIES IN CORONARY THROMBOSIS

WARREN B. COOKSEY, M.D., AND HUGO A. FREUND, M.D.
DETROIT, MICH.

THE electrocardiographic changes produced by coronary occlusion have been a matter of keen interest during the past twelve years. In 1918 Smith¹ first made electrocardiographic studies in dogs in which he had experimentally occluded various branches of the coronary arteries. In 1920 Pardee² presented "an electrocardiographic sign of coronary artery obstruction" which he felt was diagnostic. In 1928 Parkinson and Bedford,³ and in 1929 Levine and Brown⁴ published their extensive studies in this disease. With the completion of this work, much data was available for an understanding of the electrocardiographic findings in coronary occlusion. It was at first believed that all cases would be associated with positive electrocardiographic changes, but instances have been disclosed of undoubted coronary occlusion in which no electrocardiographic evidence seemed present. To further complicate the picture, Scott, Feil and Katz⁵ pointed out that positive ST changes in the electrocardiogram were sometimes present in pericardial effusion and in pericarditis. Kountz and Gruber⁶ were able to produce experimental ST changes by the production of anoxemia. They did this by placing their animals in an atmosphere containing insufficient oxygen and also by powerful doses of a vaso-constrictor. More recently Shearer⁷ has published a case of pneumonia in which positive ST changes were found in the electrocardiogram.

We believe that the above findings may all be explained on the basis of delayed coronary flow or the result of a general or local anoxemia; furthermore, it has been our impression that if more frequent electrocardiographic studies were made on undoubted cases of coronary thrombosis, it would be possible to demonstrate changes which might not be brought out by single or occasional tracings. With this object in mind, we have attempted to make serial studies on every case of undoubted coronary thrombosis coming to us in private practice during the last two and one-half years.

It has been our purpose to ascertain: (1) If any additional diagnostic criteria could be found by a more detailed study of such cases; (2) The degree of variability of the electrocardiographic waves found during the course of the disease; and (3) What if any prognostic significance could be attached to the various findings.

We have followed a total of twenty-four cases and in every instance, there has been electrocardiographic evidence of the disease. In the ac-

companying plates, thirteen of these cases are shown. Those not reported here, represent hearts in which only a single typical tracing was obtained before death, cases in which the study was incomplete, or tracings so characteristic as to be merely a repetition. We have not attempted to reproduce every tracing taken in a series, but have selected only those which were most significant. It will be noted that the tracings vary a great deal from time to time. If we rely only on the findings of a single electrocardiographic examination, such a tracing would be very misleading. This may be said to be particularly true if one is seeking only ST changes or the typical cove-shaped T-waves first described by Pardee. While both of these findings are of very frequent occurrence in coronary thrombosis, it is our feeling that they are by no means always present at the time a tracing is first made. It is only by serial study that evidence of the nature of the patient's complaint is obtained. The following is a summary of the electrocardiographic findings which we have found diagnostic of coronary thrombosis.

1. *Deflections from the Iso-electric Level of the ST or RT Interval.*—This finding when of real significance is usually quite marked and a deviation must always be present in at least two leads. It is sometimes found in three leads. In this series there is deviation upward in Leads II and III in five cases (1, 4, 5, 9, 13). There is deviation downward in Leads I and II in one case (2); upward in Lead I, downward in Leads II and III in two cases (3, 6); and in one case there is deviation downward in Lead I and upward in Leads II and III (10). The RT changes are of striking character in every instance with one exception, which is noted in Case 3. In this case there is very slight RT change upward in Lead I and downward in Lead II with some possible change downward in Lead III. It will be noted in this case that it was only after the end of forty-four hours that the slight ST change gave way to the cove-shaped T-wave in Lead I. In a few cases the RT deviation seems to reappear after the acute occlusion as in Cases 1, 4 and 5. As a rule however, the RT deviation usually disappears in a few hours or days and is replaced by the inverted cove-shaped T-wave or some other significant deviation.

2. *The Cove-Shaped Negative T-Wave*, sometimes called the "Pardee T-wave of cardiac infarction," appears frequently. However, in this series, there are two cases of proved coronary thrombosis in which a typical Pardee T-wave did not appear at any time even where tracings were taken a few hours after the onset (5, 8). In Case 8, an autopsy was available. An extensive infarction was present in the left ventricle, yet other changes than RT deviation or a Pardee wave were present in the electrocardiogram. In Case 3, the cove-shaped negative T-wave appeared in forty-four hours after the attack but in Case 6, the so-called typical T-wave did not appear for sixteen days. There are many variations between these two extremes. As has been pointed out by Parkin-

son and Bedford, the Pardee T-wave may entirely disappear after once being present. In this series it had entirely disappeared in four cases; in six months, ten months, twelve months and fourteen months respectively. In four cases the Pardee T-wave is still present at the end of eighteen months, twenty months, twenty-four months and thirty months, respectively.

3. *Changes in Amplitude.*—(a) The most frequent alteration occurs in the QRS complex, as has been noted by Wearn^s and others. To be of diagnostic significance, this change must take place in a short period of time. It is frequently of marked degree and when the fall is extreme, may be interpreted as an indication of extensive myocardial damage. In cases in which the QRS fell to one or two millimeters, a grave prognosis has usually been substantiated. We have noted a marked fall in amplitude in seven cases (4, 6, 8, 13 and three cases not included in this paper).

(b) While a change in the T-wave is frequently demonstrated from hour to hour, or day to day in coronary occlusion, this fact has not been sufficiently emphasized. We believe that a marked flattening of the T-wave without other changes occurring in a brief period of time is also an indication of a sudden profound change in the integrity of the myocardium. We know of no process which can produce this sudden change except coronary occlusion. While the flattening out of the T-wave is usually associated with a lowering of amplitude of all portions of the curve, this is not necessarily true. In Cases 4 and 8, this marked flattening out of the T-waves is evident.

CASE HISTORIES

CASE 1.—A male physician, aged 65 years, had been in good health previously. His systolic blood pressure was usually 135-145 mm. On December 30, 1928, he had just awakened when he was seized with severe substernal and precordial pain. He became pulseless and cyanotic. A nearby physician who came found him in a state of collapse. After the administration of morphine, his pain was relieved and he complained only of weakness. He refused to stay in bed longer than two weeks and in three weeks he was walking outside. Since the attack he has remained quite well, but suffers stenocardia on walking fast or against a cold wind.

CASE 2.—A business man aged 69 years, who had suffered an attack of transient hemiplegia in 1918. His blood Wassermann was strongly positive at that time. He had received vigorous anti-luetic treatment when he would submit. On November 15, 1928, he was awakened at 5 A.M. by a severe precordial pain. When seen by us shortly afterward, he was pulseless, his extremities were cold and his blood pressure was below 100 mm. systolic. After the administration of morphine, and caffeine sodium benzoate, his condition improved. His convalescence was prolonged but uneventful. At times since then he has had attacks of severe weakness and a sensation as if he would faint. We considered these attacks due to his cerebral syphilitic endarteritis. More rigid specific treatment has stopped them. There has never been any evidence of aortitis or aneurysm in this case.

CASE 3.—A Jewish housewife aged 49 years. Her average systolic blood pressure was 210 mm. and she was markedly overweight. She also had a moderately large

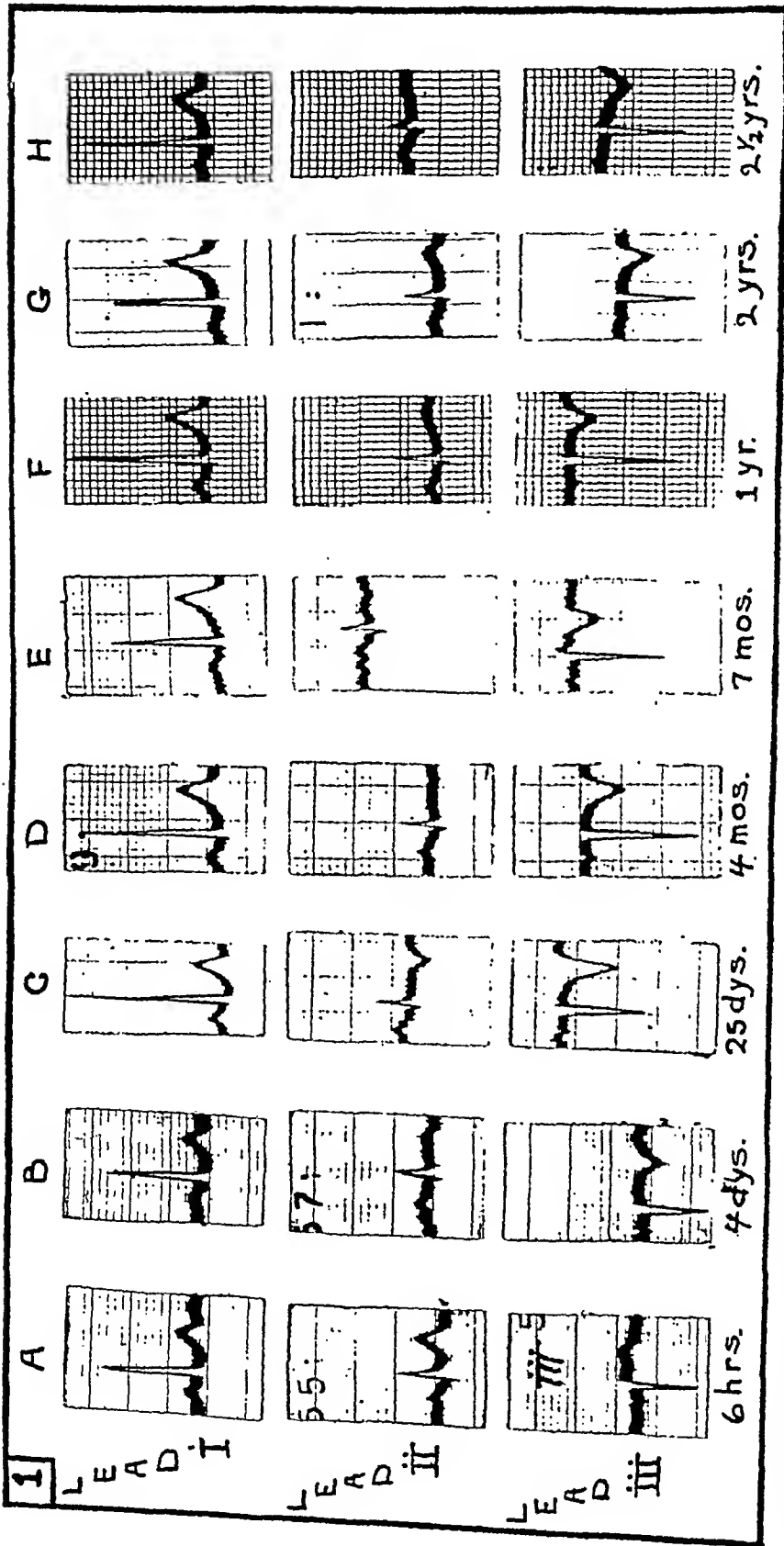


Fig. 1.—4, six hours after attack; B, four days after; C, twenty-five days after; D, four months after; E, seven months after; F, one year after; G, two years after; H, two and one-half years after. Note high take-off of rT in Leads II and III in A. The cove-shaped T-wave which develops in Lead II is gradually lost but T3 remains deeply negative with a reciprocal high peaked and positive T1. This is often a permanent residuum of coronary occlusion.

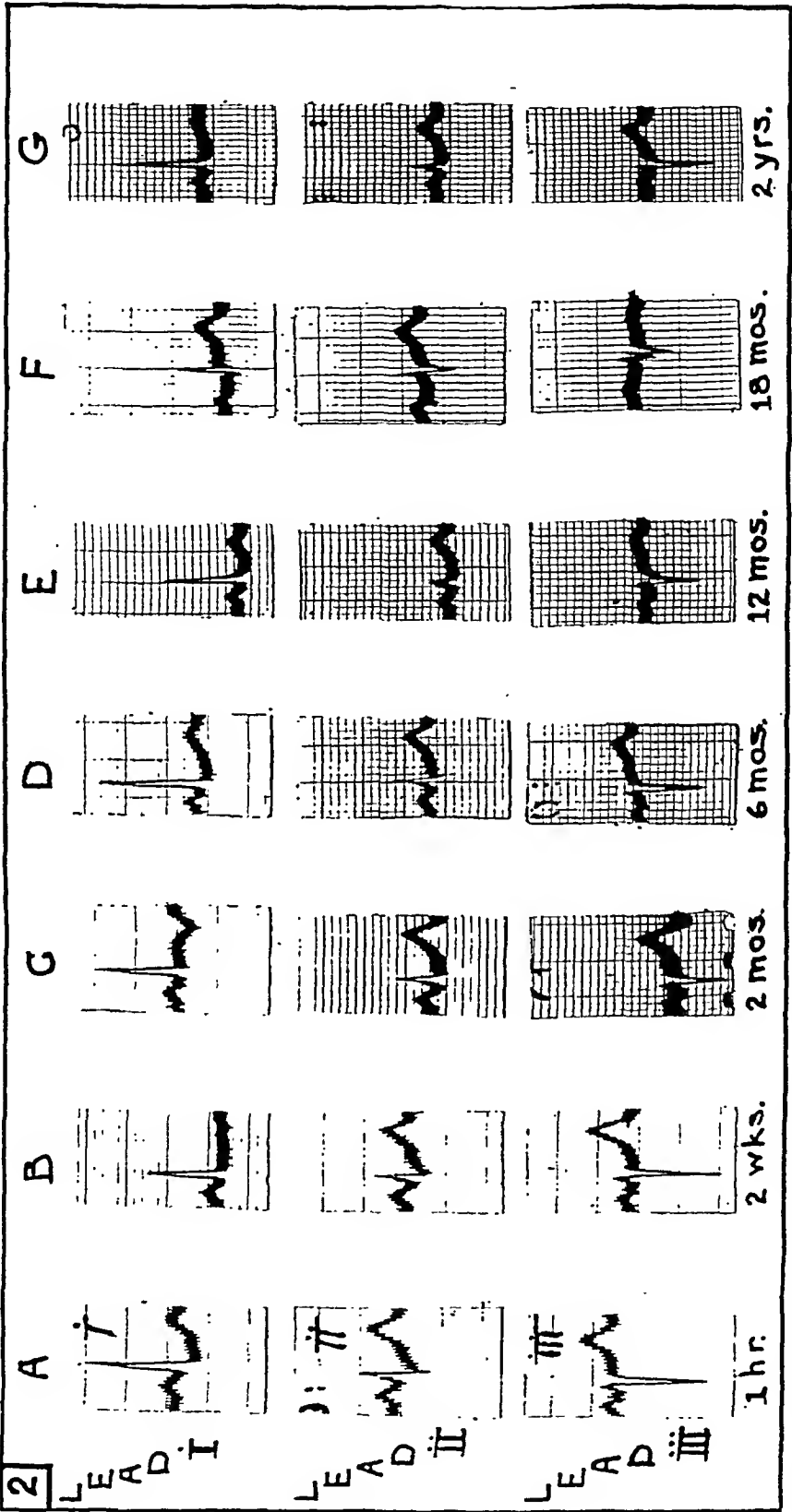


Fig. 2.—4, one hour after attack; B, two weeks after attack; C, two months after; D, six months after; E, twelve months after; F, eighteen months after; G, two years after. Note the positive RT changes in A. Here we find a cove-shaped negative T I appearing two months after the occlusion. The final tracing is normal in appearance.

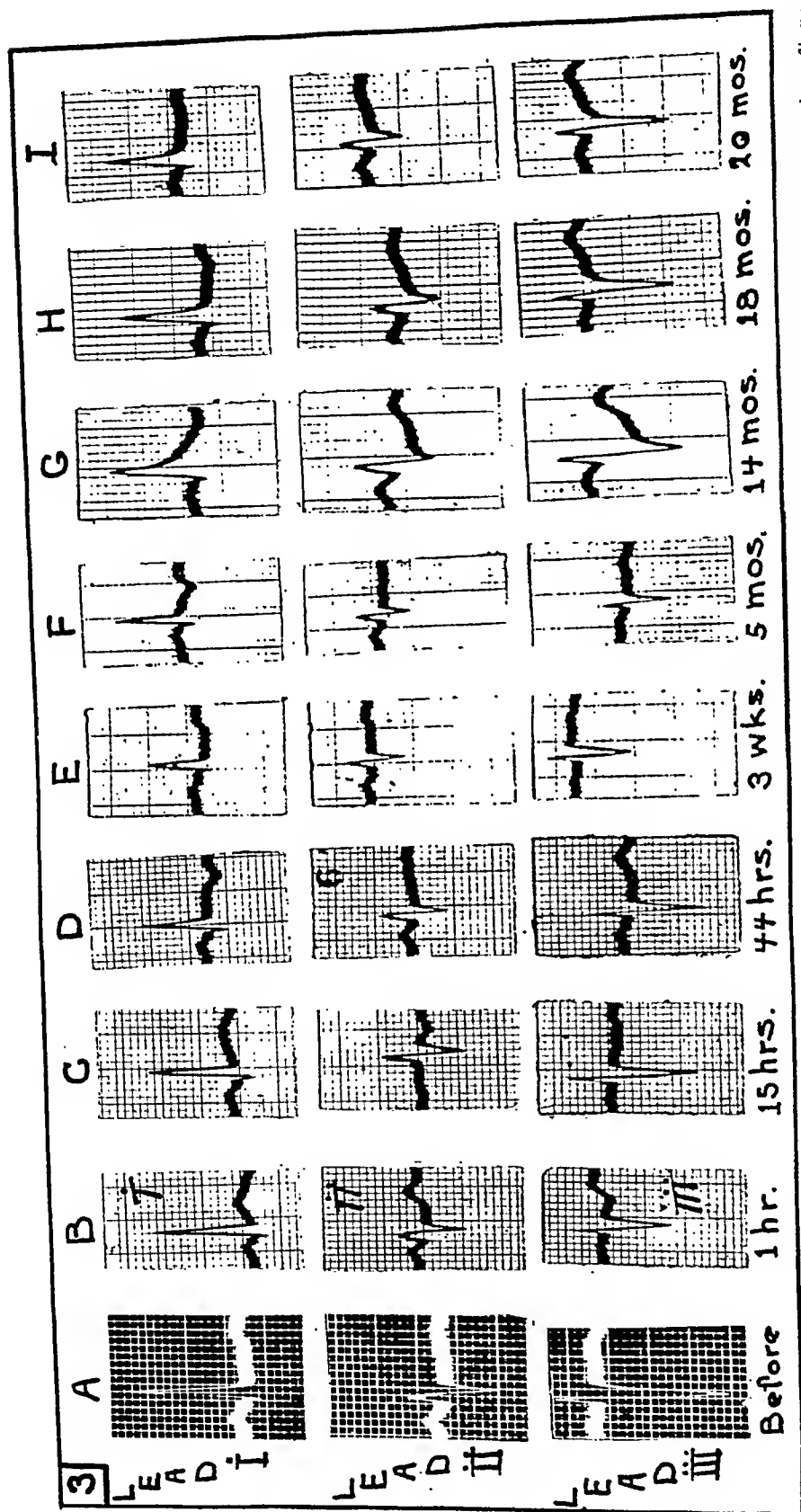


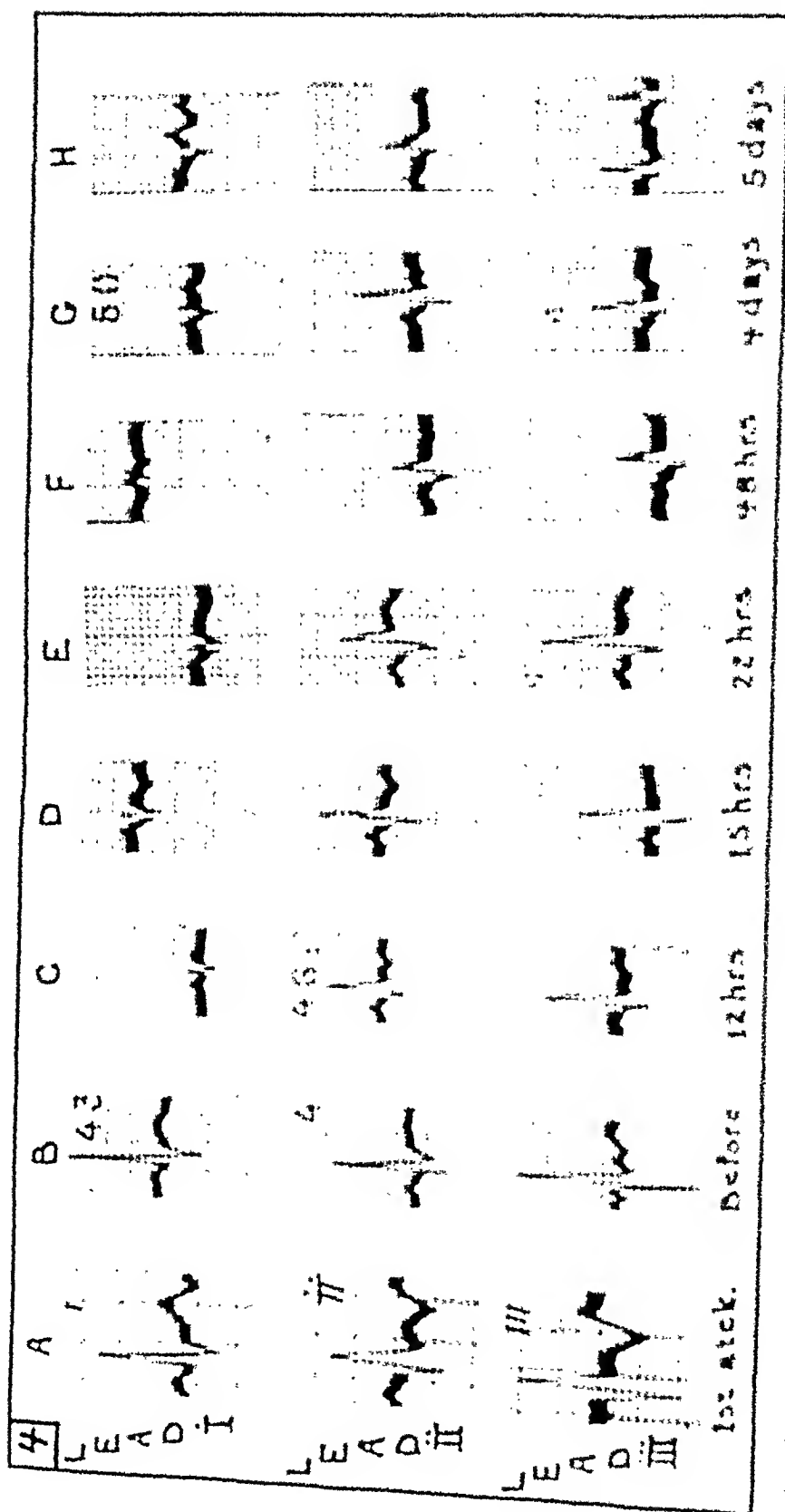
Fig. 3.—A, four months before attack; B, one hour after attack; C, fifteen hours after; D, forty-four hours after; E, three weeks after; F, five months after; G, fourteen months after; H, eighteen months after; I, twenty months after. Note the slight elevation of RT in Lead I and depression in Lead II in B and C. It is only at the end of forty-four hours that the cove-shaped T-wave appears. A flattening out of T I is noted, preceding the development of the cove-shaped negative T. G represents another small occlusion (see history).

thyroid adenoma and had taken thyroid extract at one time. At 4 A.M., March 28, 1929, she was awakened by substernal and precordial pain with radiation to the left arm. In a few minutes she vomited and insisted she was going to die. When seen in less than thirty minutes, she was pulseless, cyanotic and covered with beads of cold perspiration. Her blood pressure could not be obtained and there were numerous râles at both bases. After the administration of morphine (gr. $\frac{1}{2}$) and caffeine sodium benzoate, her condition improved. For two days following, her temperature reached 100.5 in the afternoon. No friction sounds were heard. Fourteen months later she had another mild attack for the relief of which a total of one grain of pantopon was required. On exertion she still complains of stenocardia and her systolic blood pressure is above 200.

CASE 4.—A general insurance agent aged 53 years. Fourteen months before he had suffered an attack of chest pain and subsequent fever. Coronary thrombosis was not diagnosed at that time. He was seen four weeks later by another physician who took an electrocardiogram and insisted that the patient give up his work for one year. Three days before he was first seen by us, he avoided an automobile accident only by strenuous effort on his part. Following this near accident, he felt some chest discomfort and decided to have a physical examination. He was ordered to bed but two days later we were called in emergency to his home where we found him suffering intense substernal pain. He was cold and already marked cardiac decompensation was present. His condition was grave for two days following this, but improvement occurred and he seemed to be progressing very satisfactorily. Signs of cardiac failure reappeared and five days following the onset of severe pain he died. Autopsy revealed an old and partially canalized thrombosis of the right descending coronary, a large infarction of the anterior wall of the left ventricle and a fresh thrombosis of the descending left coronary artery about 2 cm. from its union with the left circumflex artery. The coronary vessels were not markedly sclerosed as a whole but at the site of the fresh thrombus, marked calcification was present for a distance of 1.5 cm.

CASE 5.—Automobile executive aged 39 years. He had rheumatic fever for three months at the age of 14 years, but considered himself unusually well. Two years previously, a general physical examination failed to reveal any abnormality of heart or blood pressure. On the morning of August 16, 1929, he was awakened by severe precordial pain of great intensity which radiated to both shoulders and down both arms to his finger tips. He said he felt as if he were going to die. After two hours, however, he had only dull pain and was finally driven to the factory where he was again seized with severe pain and collapsed. He was given morphine and when his condition permitted, he was taken to the hospital. At entry six hours after the onset of pain, his temperature was 100 and his pulse 100. The total white blood count was 19,200. Physical examination revealed very faint heart sounds and a blood pressure of 110 systolic and 80 diastolic. The following day a friction sound was audible over a limited area at the fourth interspace to the left of the sternum. In 48 hours his temperature was normal and he felt very little discomfort. Five weeks after the onset he insisted on going to the bathroom after which precordial pain recurred. For the first time râles were audible in both bases. A more prolonged convalescence was uneventful. He now is moderately active and free from pain.

CASE 6.—Real estate man aged 53 years. He had been a very heavy smoker all his life and at times a heavy drinker. Following a drinking bout in 1929, his blood pressure was found to be 170 systolic and 100 diastolic, but subsequently never exceeded 150 systolic. His apartment was on the fourth floor but in spite of the fact that there was no elevator, he did not complain of cardiac symptoms. On the evening of October 12, 1930, he was lifting a heavy trunk when he felt



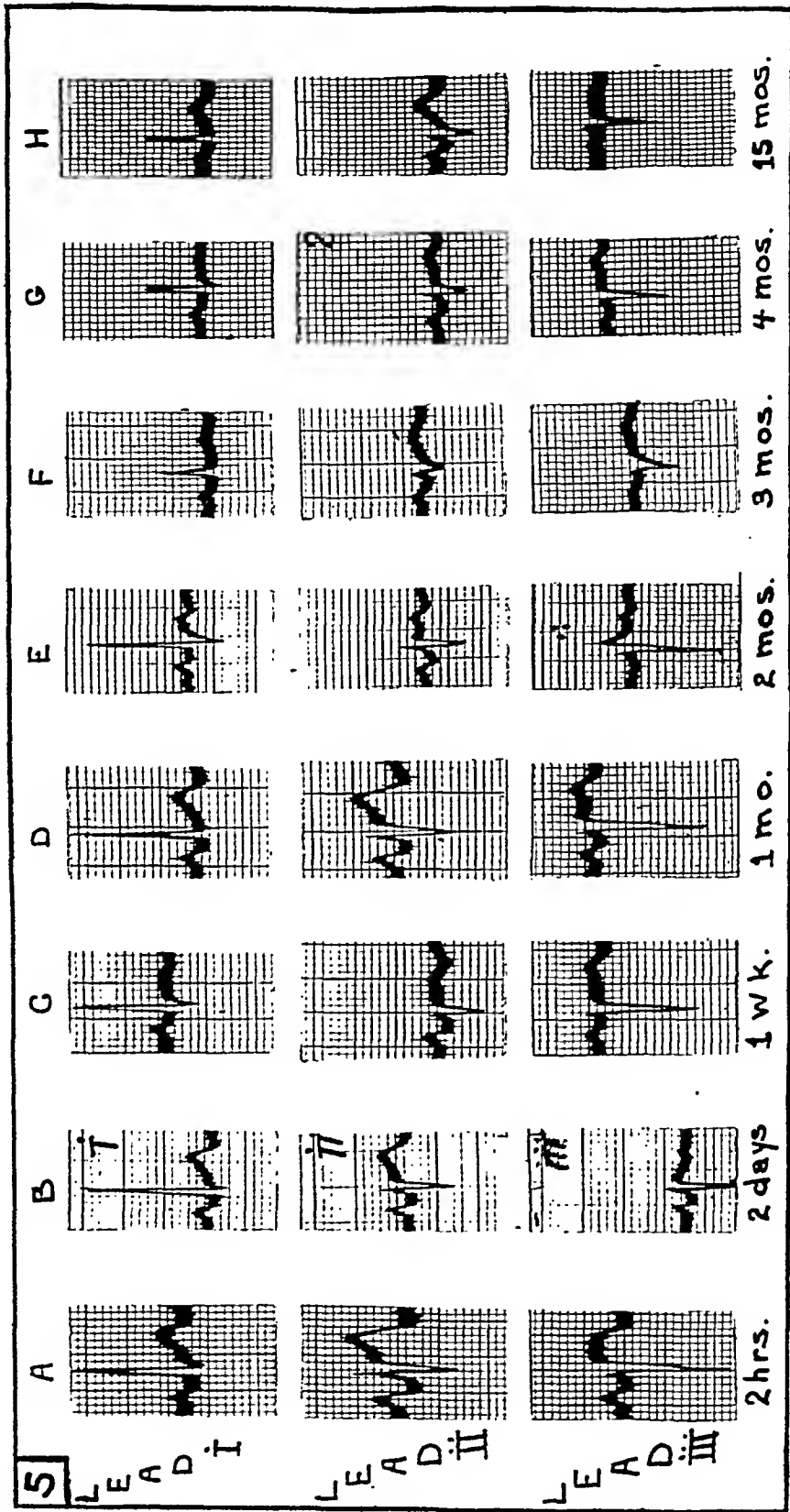


Fig. 5.-A, two hours after complete collapse; B, two days after; C, one week after; D, one month after; E, two months after; F, three months after; G, four months after; H, fifteen months after. Note in A the high take-off of ST. This is lost but reappears one and two months after the occlusion. A diphasic slightly cove-shaped T 1 and T 2 is present one week after the attack but does not appear thereafter. The great variability of findings are well shown.

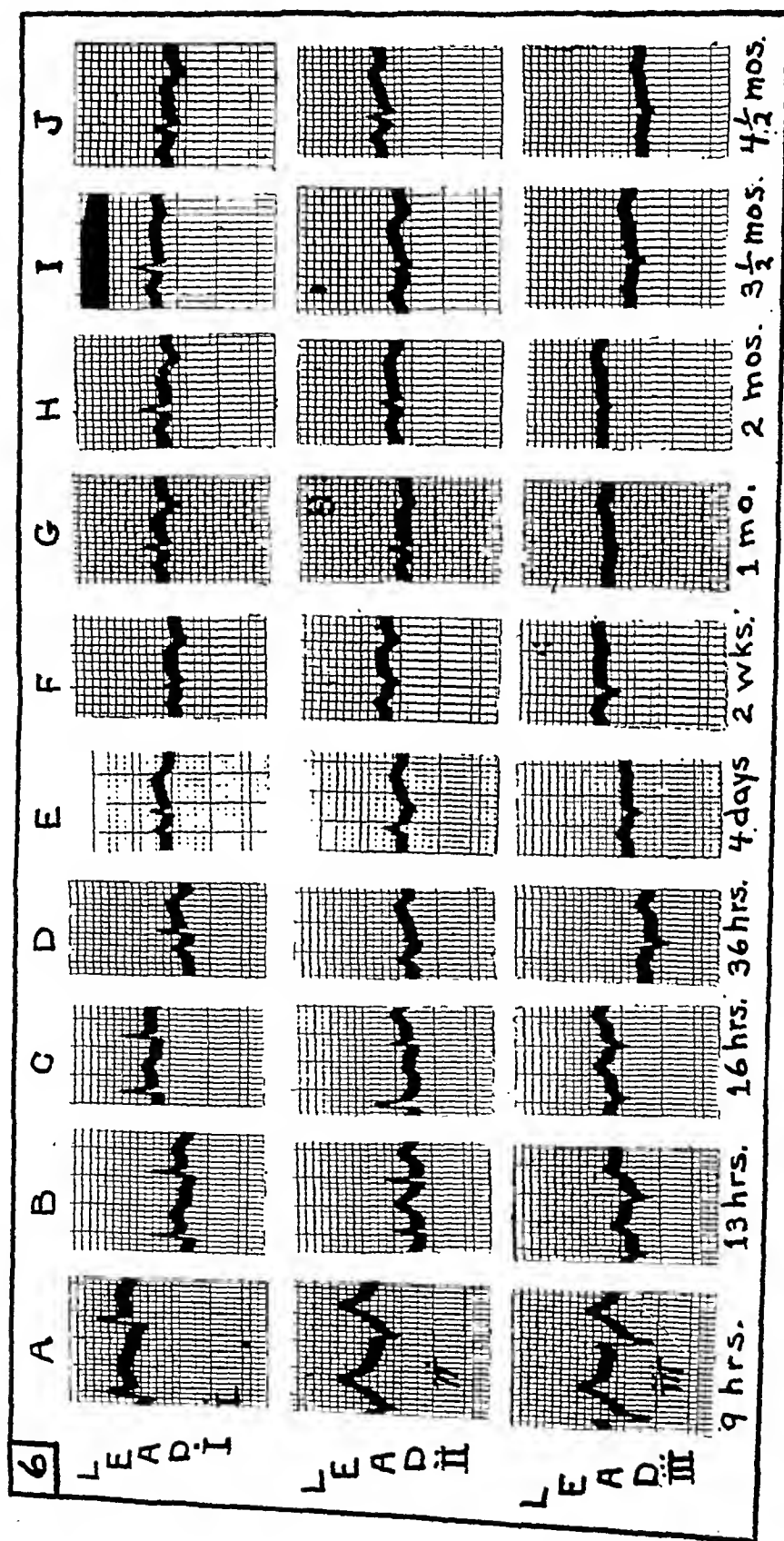


Fig. 6.—A, nine hours after onset of pain; B, thirteen hours after; C, sixteen hours after; D, thirty-six hours after; E, four days after; F, two weeks after; G, one month after; H, two months after; I, three and one-half months after; J, four and one-half months after. Note the typical RT elevation in the early curves and the rapid fall in amplitude of the QRS. The cove-shaped T-wave in Leads I and II does not appear for sixteen days after the occlusion and has not disappeared in Lead I at the end of four and one-half months. This is the only case in which the voltage has fallen as low as is found in F, that has survived the attack.

some chest discomfort. This slowly increased and at 1:00 A.M., October 13, he walked downstairs and to a near-by hospital where the night doctor examined him but found nothing of significance. One grain of codein was given but without the slightest benefit. At 6:00 A.M. after five hours of agony, one of us was called to see him. He did not in any respect seem acutely ill. His color was good, the pulse 100, blood pressure 140 systolic and 90 diastolic. The heart sounds seemed as usual and there was no pulmonary congestion. He had no rise of temperature. One-fourth grain of morphine was given but in thirty minutes he was no better so that the dose was repeated with gradual relief. He localized the pain in the region of his sternum at about the level of the fourth interspace; there was no radiation. Entirely on the basis of the intensity of his pain, coronary thrombosis was diagnosed. During the first forty-eight hours his condition became critical. His temperature averaged 100.5 for four days. After this he felt very well. He was not allowed out of bed for ten weeks. His condition is very satisfactory at the present time, although he has not been allowed to leave his rooms.

CASE 7.—A housewife aged 59 years. She had had epileptic seizures for many years but of very infrequent occurrence. At times she complained of some dyspnea on climbing stairs but physical and electrocardiographic examination was normal. On the evening of April 2, 1928, she was alone in her home when burglars entered and at the point of a gun tied her to the bedpost. After they had looted the house, she released herself and ran screaming to her neighbors. After much excitement, she retired at 1 A.M. but one hour later had an epileptic seizure. She appeared very weak so a physician was called who found her almost pulseless. On the following day she had a very irregular pulse, a temperature of 101 F., and profuse râles were found in both bases. For three days she complained of slight pain just beneath her clavicle on the left. Four days elapsed before coronary occlusion was diagnosed and then only after the electrocardiogram was seen. At the present time she has some palpitation and dyspnea on climbing stairs, but no precordial pain.

CASE 8.—A business man aged 70 years had complained of bronchitis for many years but had been unusually active and well. Following coitus on June 22, 1930, he felt some chest discomfort and by the next morning, this had increased. Morphine was finally required for relief, although his distress was not well defined. His blood pressure gradually fell to 100/60, the heart sounds were very faint and râles appeared in both bases. His condition grew gradually worse, but after three days was much improved and he felt well. His blood pressure remained between 90 and 100 systolic. The heart sounds improved and the râles disappeared from the chest. His temperature reached 101° F. during the first three days. On the second day after the onset, his white blood count was 18,000. On the morning of the seventh day as he was about to eat his breakfast, he suddenly clutched his throat and was dead in a very few seconds. At autopsy the coronary vessels were found to be markedly sclerosed throughout and there was a softening thrombus completely occluding the left descending branch. There was an extensive infarction of the left ventricle.

CASE 9.—Female, aged 70 years. She had complained of precordial and chest pain after excitement or exertion since November, 1928. Physical examination and electrocardiogram revealed no abnormalities but the blood pressure was 170 systolic and 90 diastolic. April 3, 1930, she complained of vise-like pain which came on after attending a moving picture. Again examination revealed nothing. May 1, 1930, while visiting in Pittsburgh, she was seized with precordial pain which required morphine every three hours to control. On May 23, she returned to Detroit where we noted an alteration in the electrocardiogram (Fig. 9-B). She remained quite well although she often complained of heaviness across her chest. On Novem-

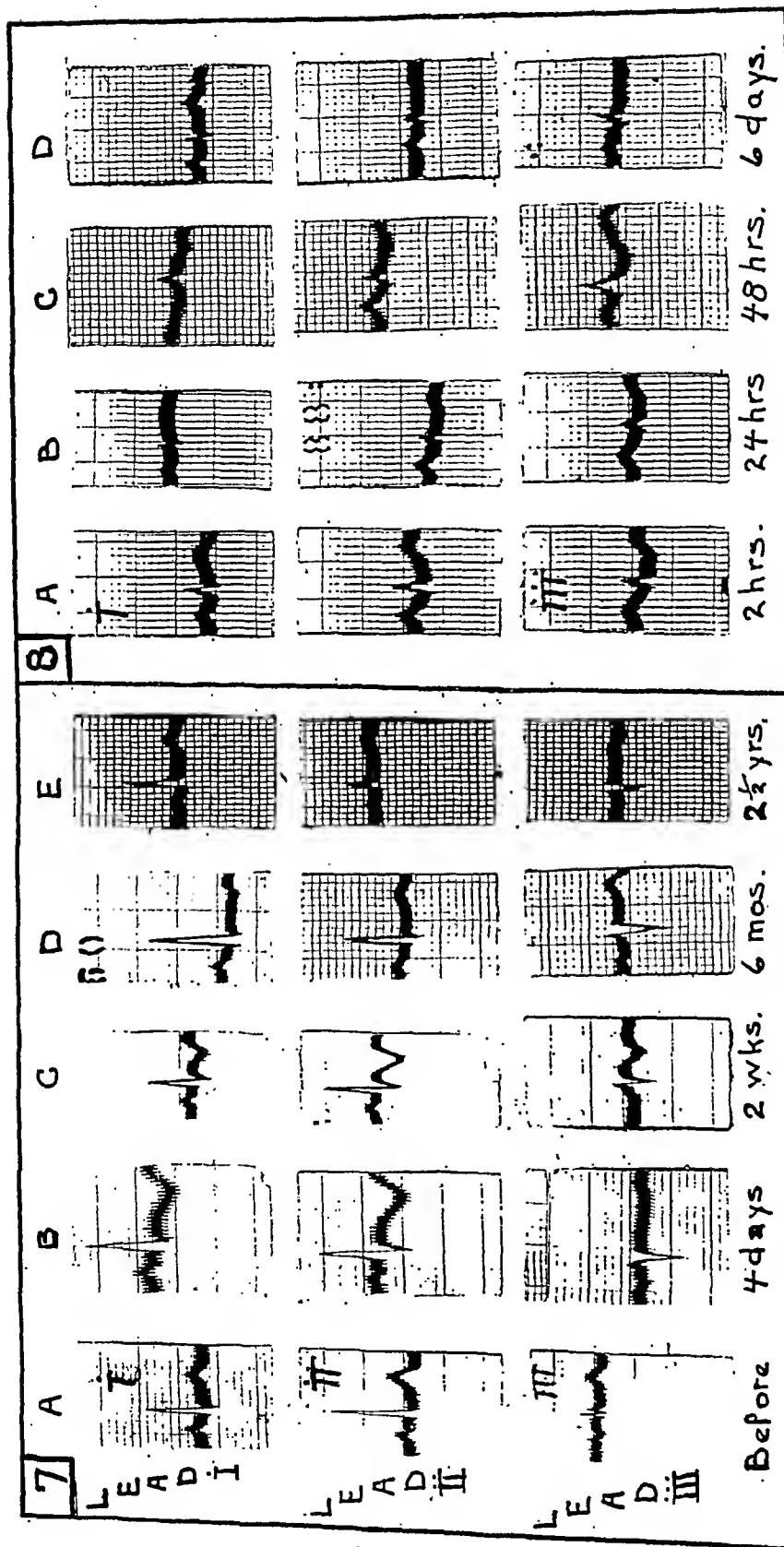


Fig. 7.—A, six months before attack; B, four days after attack; C, two weeks after attack; D, six months after attack; E, two and one-half years after attack. Note the deeply negative cove-shaped T-waves in B and C. This is a typical cove-shaped T-wave type of curve.

Fig. 8.—A, two hours after attack; B, twenty-four hours after attack; C, forty-eight hours after attack; D, six days after attack; twelve hours before death. Note presence of T-waves of nearly normal amplitude in A. In this case the T-waves flatten out in a very short time as the case progresses. The amplitude of the QRS also diminishes rapidly and reaches a low level. The patient's attack was not typical and entirely on the basis of the rapid fall of the T-waves and the rapid fall of QRS amplitude, a presumptive diagnosis of coronary thrombosis was substantiated.

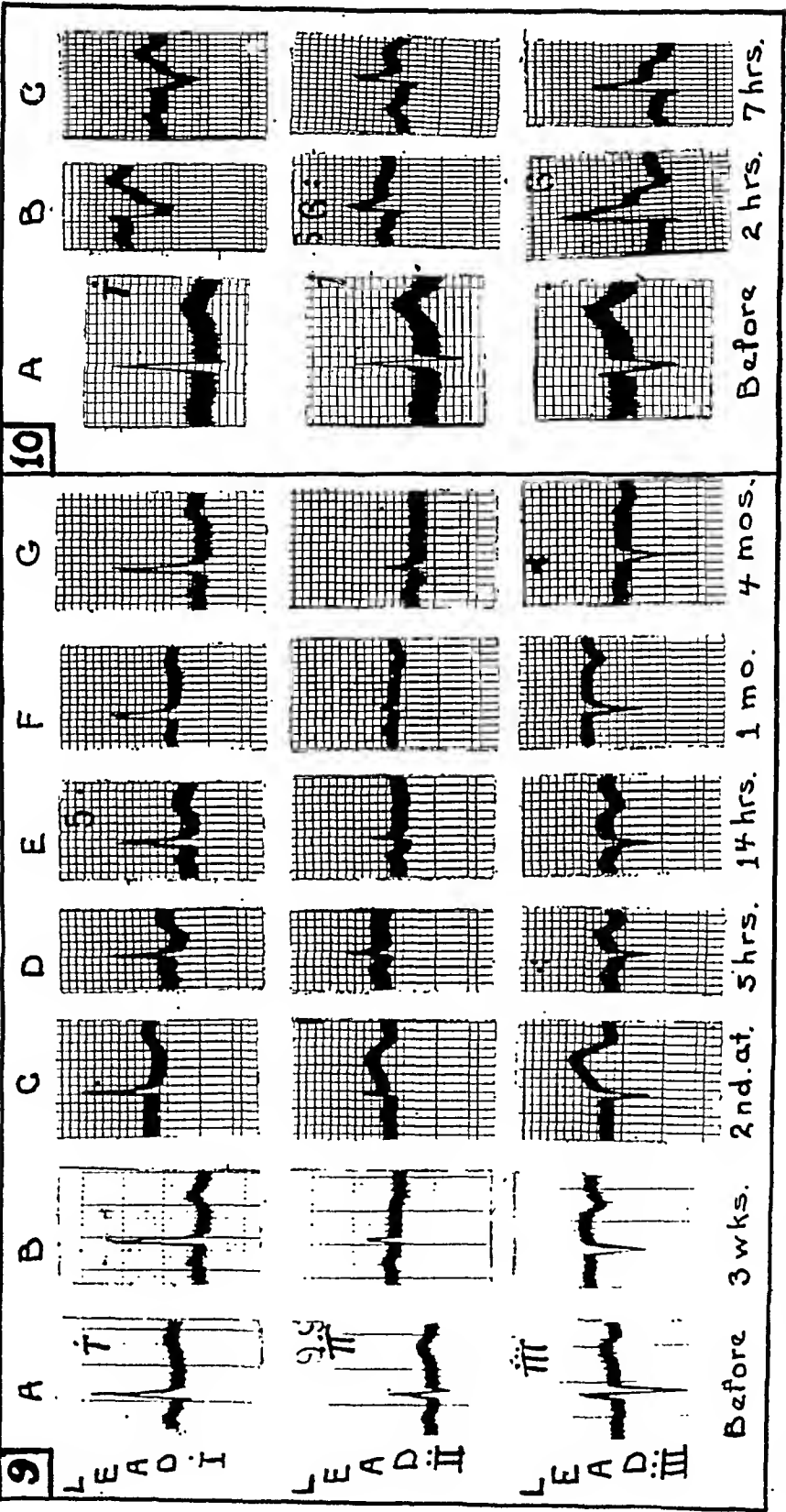


FIG. 9.—A, three weeks before first attack; B, three weeks after; C, during second attack; D, five hours later; E, fourteen hours later; F, one month later; G, four months later. The change in T 3 with a slightly higher and sharper T 1 is the only residuum of the first attack. In this series the RT changes are unmistakable and characteristic. Only at the end of thirty days does a cove-shaped T 2 appear following the second infarction.

FIG. 10.—A, one year before attack; B, two hours after attack; C, seven hours after attack, four hours before death. Following the occlusion the typical RT changes are produced. The PR and QS intervals also are prolonged. In this series note RT and ST changes of striking degree in every lead.

ber 1, she began to have precordial pain with radiation to the left arm especially involving the left thumb. The pain was so intense that she insisted she was dying. When first seen in this attack, she was slightly cyanotic, her pulse was 100 but perfectly regular. The blood pressure was 90 systolic and the lungs clear. Her condition rapidly grew worse and in twenty-four hours her temperature had risen to 100.8 degrees F. and her total white blood count was 12,000. Râles were never detected in the lungs and a friction sound was never audible. In four days she was comfortable although she complained of great weakness. She is still convalescing.

CASE 10.—A business man, aged 70 years. He had complained of precordial pain for two years and his blood pressure was usually 180 systolic and 100 diastolic. He frequently used nitroglycerine for the relief of the stenocardia. On the morning of October 11, 1930, he was awakened at 5:00 A.M. with severe pain in his chest. When seen he was sitting up in bed presenting the appearance of extreme anguish. His color was ashen, the blood pressure below 100 systolic, there were profuse râles in both bases and the pulse was rapid and weak. His condition slowly grew worse and fourteen hours after the onset of pain, he died. An autopsy was not obtained.

CASE 11.—A drug salesman, aged 50 years. In 1924 he was seen complaining of joint pains. At that time a systolic murmur was heard at the apex and aortic area. The blood pressure was 155 systolic and 90 diastolic. The blood Wassermann was negative. In February, 1928, he consulted us because of a dull discomfort across the upper chest which he thought was related to exertion. There was some radiation of the distress to both shoulders and arms. At this time a definite to-and-fro murmur was heard over the aortic area and the supracardiac dullness was increased. The Kolmer Wassermann was 1-3-3-0-0. He was given anti-luetic treatment for a time and was definitely improved. In September, 1928, he began to complain of precordial pain on exertion. On September 25, 1928, he was seized by excruciating and vise-like pain in the anterior chest, and was unable to get out of bed. Morphine was required for twelve hours and the following day the temperature was slightly elevated. At the present time he has stenocardia on strenuous exertion but the aortic widening and the to-and-fro murmur are unchanged. His blood pressure in December, 1930, was 120 systolic and 80 diastolic.

CASE 12.—Merchant, aged 62 years. For three years he had complained of stenocardia on exertion and had been told that he had high blood pressure and nephritis. September 24, 1930, he began to have precordial pain which was more persistent and more severe than ever before and which was not entirely relieved by nitroglycerine. His blood pressure on October 7, 1930, was 170 systolic and 100 diastolic, the heart sounds were very weak and there were râles at both bases. From then on his pressure began to fall and in two weeks had fallen to 100 systolic. There were more râles at the bases. Though he often would go several days without any precordial pain, he had three attacks of great severity. On November 10, 1930, he was awakened at 5:00 A.M. by an intense difficulty in breathing which his relatives described as of a "rattling" character. He could hardly speak and was in great anguish. In less than ten minutes he was dead. Autopsy was refused.

CASE 13.—Retired realtor, aged 75 years. For eight years he had complained of attacks of chest pain following exertion and had used nitroglycerine with some relief. On October 23, 1930, he complained of a steady and intense precordial pain which nitroglycerine did not relieve. When examined a few hours after morphine had been given, he was very comfortable, the pulse was 110, the blood pressure 100 systolic and 60 diastolic and the heart sounds of fair quality. The lungs were clear. On the following day râles were heard at the base of the lungs. He often

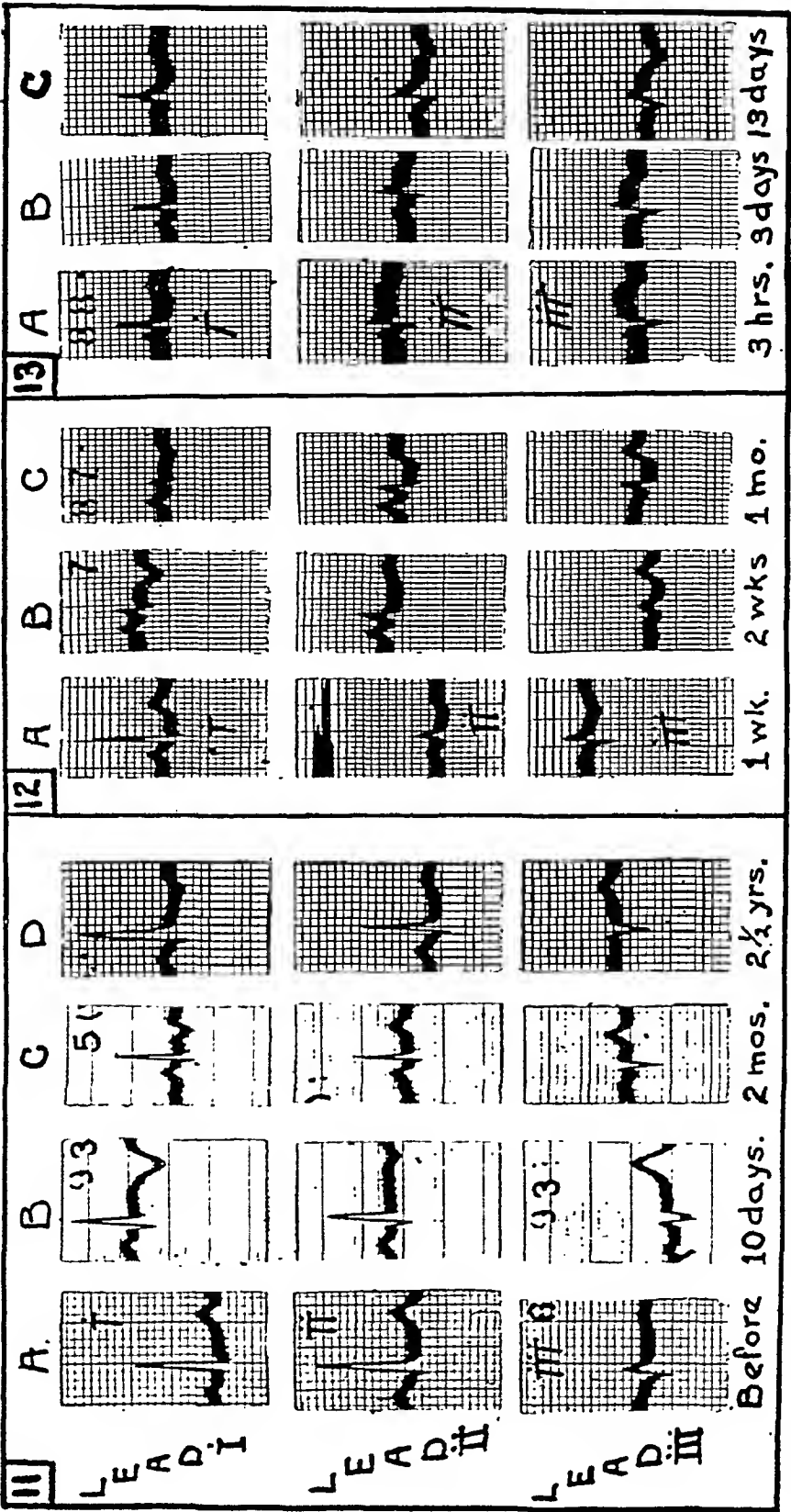


Fig. 11.—A, three and one-half months before attack; B, ten days after attack; C, two months after attack; D, two and one-half years after attack. The reciprocal T 1 and T 3 of magnified amplitude, as compared with the previous curve, is apparent in B. At the end of two and one-half years the T 1 change is the only residuum.

Fig. 12.—A, one week following first persistent pain; B, two weeks after; C, one month after and five days before sudden death. The progressive changes are evident in this case; the occlusion was either a slowly increasing one, or multiple occlusions. The falling amplitude indicated a poor prognosis.

Fig. 13.—A, three hours after attack; B, three days after; C, thirteen days after and one week before sudden death.

required morphine for relief of pain during the first week of this illness and afterward for restlessness. His condition steadily failed and he died three weeks after the onset of his severe pain.

COMMENT

While we are not prepared to say that characteristic electrocardiographic changes always occur following acute coronary occlusion, nevertheless it would seem that when serial studies are made, the proportion of positive findings is extremely high. In twenty-four consecutive cases studied serially, thirteen of which are shown herein, there have been positive electrocardiographic changes present in every case. As has been frequently shown in the past, the most common changes are RT deviation and the cove-shaped negative T-wave. The RT deviation has occurred in eleven out of sixteen cases and the cove-shaped negative T-wave has occurred in twelve out of sixteen cases.

Aside from the two more frequent findings just mentioned, we should like also to emphasize the importance of a marked fall in amplitude of the QRS complex. When there is available a previous curve for comparison, or when a marked fall occurs in a few hours' time, then coronary occlusion with subsequent myocardial softening may well be suspected. In this series a marked fall in amplitude is noted in seven out of sixteen cases. In one case it was of very real diagnostic benefit (8), for the onset of the patient's illness was not typical and when first seen he did not seem gravely ill. The first electrocardiogram, however, revealed an irregular rhythm and very low QRS voltage. In less than twenty-four hours this low amplitude dropped to a lower level. After remaining low for six days the patient seemed clinically well but died suddenly on the seventh day of his illness.

Changes in the T-wave were very frequent in the course of this serial study. Before a typical cove-shaped negative T-wave appears, there often occurs a flattening out of the T-wave. When there is a marked fall in amplitude of the QRS as in Cases 4 and 8, the T-wave suffers similarly by its flattening out. We feel that such a change occurring in the course of a few hours can only mean sudden profound damage to the myocardium. Acute coronary occlusion with infarction is without question the most common cause of such an event. Usually a poor prognosis is indicated where a marked fall of amplitude of the QRS either persists at a very low level or is constantly progressive beyond the first week or ten days. Four such cases were observed and only one of them (6) has survived.

SUMMARY

Serial studies were made on twenty-four cases of acute coronary occlusion. Positive electrocardiographic evidence is present in every case. The importance of taking consecutive electrocardiograms in suspected cases is emphasized. The changes of diagnostic significance are:

1. Deviation of the RT or ST interval. This change occurred in 11 of sixteen cases.

2. Development of the cove-shaped negative T-wave, first described by Pardee. This change occurred in twelve of sixteen cases.

3. Marked fall in amplitude of the QRS complex in a short space of time. This occurred in seven of sixteen cases.

4. Flattening out of the T-wave in a brief period of time. This change occurred occasionally preceding the development of the cove-shaped negative T-wave. It was marked in two cases which did not develop the typical cove-shaped T.

When a marked or progressive fall in amplitude of the QRS complex is seen, a poor prognosis is strongly suggested. Four cases revealed such a change and only one has survived the attack.

REFERENCES

1. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918. Also: Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch. Int. Med.* 32: 497, 1923.
2. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26: 22, 1920.
3. Parkinson, J., and Bedford, D. E.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14: 3, 1928.
4. Levine, S. A., and Brown, Chas. L.: Coronary Thrombosis, Its Various Clinical Features, *Medicine* 8: 245, 1929.
5. Scott, R. W., Feil, H. S., and Katz, L. U.: The Electrocardiogram in Pericardial Effusion, *AM. HEART J.* 5: 68, 1929.
6. Kountz, Wm. B., and Gruber, Chas. M.: Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
7. Shearer, M. C.: Plateau R-T in a Case of Lobar Pneumonia, *AM. HEART J.* 5: 801, 1930.
8. Wearn, J. T.: Thrombosis of the Coronary Arteries, With Infarction of the Heart, *Am. J. M. Sc.* 165: 250, 1923.

FACTORS FAVORING THE ONSET AND CONTINUATION OF RHEUMATIC FEVER*†

HOMER F. SWIFT, M.D.
NEW YORK, N. Y.

DURING the past three decades our ideas concerning rheumatic fever have undergone striking evolution, as evidenced by the change in nomenclature from acute articular rheumatism to acute rheumatic fever, and finally to rheumatic fever. True it is that the older terms still hold, and rightly so when used to describe particular forms of the infection; but too often one is employed synonymously with another. It is unfortunate that with increasing knowledge of the condition there cannot be devised a new term sufficiently extensive to embrace all of its manifestations, yet distinctive enough to separate it as a nosological entity. The introduction of the terms "infectious rheumatism"¹ and "rheumatic granulomatosis"² are attempts in this direction; but having only pathological or bacteriological significance they offer little if any advantage over the term rheumatic fever, which at least has background in clinical experience.

Objections to the use of this term are twofold: (1) The adjective "rheumatic" to most persons signifies arthritis or muscular pain, and (2) some of the manifestations of activity—notably chorea—are frequently not accompanied by fever. To this one may reply, first, that the original meaning of the term "rheuma" was a morbid process flowing from one organ or tissue to another; hence it still retains its descriptive value; and, second, that regular consistent use of the thermometer would reveal some degree of pyrexia during certain periods of most attacks; therefore, fever still remains one of our most valuable guides of persisting infection.

Another point deserves attention; if the term rheumatic fever is substituted merely for the expression, acute articular rheumatism, our nomenclature has suffered a loss, because the second signifies acutely swollen joints. When, on the other hand, it is used to include all of the manifestations of the infection in the same manner as tuberculosis includes all types of the disease induced by the tubercle bacillus, then does it have distinct descriptive value.

To many it seems well to delete the word acute because in the majority of cases the infection is long-standing. Only when rapidly fatal, or in those cases with a monocyclic course may the adjective

*Read before the New York Academy of Medicine as part of the Graduate Fortnight, October 30, 1930.

†From the Hospital of the Rockefeller Institute for Medical Research, New York.

“acute” be properly applied, but even then we must be certain that the infection has become permanently inactive. For example, we do not picture syphilis as acute even though the roseola disappears within two weeks; likewise it may be better not to use any single manifestation of rheumatic fever as an index of chronicity.

Historically the conception of rheumatic fever began with rheumatic polyarthritis; a century has elapsed since the recognition of the importance of involvement of the valvular endocardium; fifty years ago the nature of the subcutaneous nodule was noted; twenty-five years later its analogue in the submiliary myocardial nodule—the Aschoff body—was described; and within the past decade the extent of the vascular lesions has been appreciated. In the meantime with an improvement in the general economic state of society, together with extensive use of salicylates, the clinical picture has apparently changed. Hyperpyrexia rheumatica has become a medical curiosity, and according to old clinicians rheumatic polyarthritis is less severe. But whether there has been a corresponding amelioration in carditis and chorea one may well doubt. Knowledge gained from contemporary graphic methods of recording cardiac abnormalities renders difficult comparison with statistics obtained in other ways; but figures such as presented by Ehrström and Wahlberg³ in Helsingfors indicate that there has been no diminution in the incidence of chronic rheumatic heart disease from the administration of salicylates; and according to recent statistics it still seems that rheumatic fever is the largest single factor in the causation of heart disease.⁴

May it not then be of greater value to apply another method of historical approach, beginning in childhood and following the various manners of the unfolding of the infection, rather than to orient ourselves from the disease in adults where it is less frequent even though more acute, and where severe cardiac damage is relatively less common.

But before tracing the clinical course it may be well to reconstruct a background of histopathological tissue changes. What does the microscope show us concerning the nature of the infection? Aschoff's description of the submiliary nodules arising in the loose connective tissue septa in the myocardium furnished a structural archetype to which alterations in other tissues might be compared. The discussion which has centered about this nodule has at times diverted attention away from the fact that other lesions, possibly not quite so regular in their cellular structure, might be just as characteristic. One need only mention the subcutaneous nodule. The important factors to recall are the type of tissues and organs involved, and the manner of evolution of the lesions; one may then attempt to construct from these factors or elements a hypothesis of the nature of the infection.

In the Aschoff body there is a minute central area of broken collagen fibers, surrounded by large cells probably derived from locally stim-

ulated connective tissue. At times there are seen polymorphonuclear cells, lymphocytes and plasma cells; and finally fibroblasts leading eventually to a scar. The subcutaneous nodule shows qualitatively similar tissue injury and cellular response, but with different quantitative distribution of the component parts; the connective tissue degeneration is often more massive, the groups of large mononuclear cells are more numerous. Frequently a large nodule is apparently formed as a conglomeration of smaller nodules. In places large basophilic mononuclear cells seem to arise from vessel walls. Relatively few polymorphonuclears are present. If now we examine the joints another but related picture appears. The peri-articular tendons and ligaments show numerous microscopic areas in form of nodules or tongues, most having necrotic centers and surrounding proliferated cells. The synovia shows palisading of its lining layer, and minute foci with central necrosis with surrounding collars of cells. Diffuse infiltrations of polymorphonuclears are common. The peri-articular tissues are infiltrated with serum which in part contributes to the familiar swollen joint; and there is destruction of muscle fibers at the musculo-tendinous junctions.^{2, 5, 6} In other words, the minute focal and vascular lesions about the joints are numerous, and exudation is widespread. Involvement of the pleura and pericardium shows similar exudative tendency, but in the substance of these membranes are often foci comparable with the Aschoff bodies. In the auricular endocardium there are similar tissue and cellular changes, but these are arranged in streaks and plaques without interruption in the continuity of the lining endothelium.^{7, 8} In the valves on first sight appears another picture, for the endocardium is broken and thrombotic verrucae are often, though not always, laid down at the site of impact of the leaflets. But throughout the substance of the valve and in the chordae may often be seen broken collagen material, proliferative cells and infiltrations like that of the auricular endocardium; at times they are arranged in typical Aschoff bodies. As so beautifully shown by von Glahn and Pappenheimer⁹ and others, many portions of the vascular system are similarly involved. In the aorta focal lesions follow branches of the vasa vasorum; but smaller arteries have areas of end- and mesarteritis, always accompanied by focal destruction of connective or elastic tissue. In the peritonsillar, nasopharyngeal and intestinal blood vessels Holsti¹⁰ has demonstrated extensive endarteritis verrucosa. In the peritonsillar capsule near the points of attachment of the pharyngeal muscles MacLachlan and Richey,¹¹ Gräff¹² and others have described areas very similar to Aschoff bodies, and also in the tongue about the lingual tonsils. Gräff applies the term "primary complex" to these peritonsillar lesions because of their hypothetical rôle as sites whence the infectious agent is distributed to other parts of the body. He thinks that the pathological condition of the blood vessels supplying these lesions favors such a distribution.

The striking picture of the Aschoff body cells has, moreover, attracted attention away from what appears to be the initial injury to the connective tissue fibers. Von Glahn and Pappenheimer have frequently described the granular broken appearance of these fibers, and many have seen the fibrin-like staining infiltration in the foci; but recently Klinge¹³ claims that the primary change is a minute focal "fibrinoid swelling" of the intercellular mesenchymal ground substance; which swelling leads secondarily to a fraying out and altered staining reaction of the collagen fibers and fragmentation of the elastica. He also describes waxy degenerations of individual muscle fibers with secondary proliferation of the perimysium.

It thus appears that rheumatic fever instead of affecting any one set of organs is a disease primarily of the connective tissue, or, in Hueck's¹⁴ words, of the mesenchymal system. Those structures composed chiefly of connective tissue, and specially subject to functional stress and strain and undergoing active motion appear to be the most vulnerable. Interference with the function of these moving structures may, however, detract attention from unobtrusive lesions in other organs, such as recently described by Paul¹⁵ in a rheumatic perihepatitis with characteristic lesions in the underlying blood vessels. Rheumatic vasculitis in the kidneys has been described by Fahr,¹⁶ Evans¹⁷ and others; and symptoms of appendicitis, intimately associated with generalized rheumatic fever, point to a similar involvement of at least one portion of the intestinal tract. A constantly growing literature on pulmonary lesions in this disease indicates also how the lower as well as the upper portion of the respiratory tract may be involved.

A knowledge of the numerous points and tissues where the infectious agent attacks the body gives us another standard with which to judge rheumatic fever. If so many organs or tissues are simultaneously involved, there is every reason to suppose that they may also be individually and successively implicated. In fact, pediatricians have long appreciated the tendency of children to show first one and then another of the so-called rheumatic series;¹⁸ and that not until after the lapse of years might enough members of this series have appeared to render certain a diagnosis. Monosymptomatic signs of disease are difficult of interpretation unless sufficiently characteristic to have diagnostic specificity; for example, the various cutaneous syphilides. But in order to form correct judgment concerning visceral lesions it is often necessary to have concomitant clinical signs or specific laboratory aids.

Unfortunately in the case of rheumatic fever no specific laboratory test is at hand; some of the concomitant, easily visible manifestations, such as tonsillitis, are too nonspecific to furnish much needed assistance. But in these very nonspecific signs we may possess most important aids to understanding the nature of the infection; and in tracing the life

history of rheumatic fever it is essential to note their occurrence and then try to interpret their influence upon the course of the malady.

The causation of many chronic diseases is usually the algebraic sum of a number of factors rather than the exclusive action of any one. Infection is the result of interaction between an animal host and an infecting parasite in which many variables are too subtle for laboratory measurement. Moreover, the study of the life history of chronic disease in the patient gives us many useful hints as to the nature of the illness, and often furnishes therapeutic indications. For example, we now know that the presence of tubercle bacilli in a body does not necessarily indicate active tuberculosis. Certain environmental conditions favor the spread of the lesions; others favor their regression. Indeed, a study of these latter conditions has furnished us with some of our most important weapons against this disease; and comparable knowledge may conceivably have a similar effect in rheumatic fever.

Geographically the disease seems to be essentially one of the temperate zone. Clarke¹⁹ has recently marshalled most convincing evidence indicating that in the true tropics it is fifteen to twenty times less frequent than in Europe. Studies by the Seegals²⁰ indicate, moreover, that the infection is less common in the southern part of this country; and observations²¹ from New Orleans show that when present in the South it runs a milder course than in the North. The ultimate effect of removing rheumatic subjects to hot or dry climates is, however, still a matter for investigation.

Statistics also show that obvious rheumatic fever is from fifteen to twenty times more frequent among the laboring classes than in those forming the bulk of private practice. But many physicians can testify concerning its existence and tendency to progress in patients living under apparently ideal home surroundings. Another viewpoint has been advanced to the effect that among persons in better economic conditions the infection may have relatively more monosymptomatic forms and hence lead more frequently to cardiac damage without obvious general symptoms.

Infants and very young children are relatively free from the disease, and, even though cases appear in children of from two to four years, the curve of frequency of first attacks does not begin its steep ascent until about the age of five or six years. It then rises steadily until the period from nine to eleven years when it begins to fall. First attacks are relatively much more rare in adults than in children. The studies of Wilson, Lingg, and Croxford²² indicate, moreover, that children suffering from the infection tend to have fewer obvious relapses after the age of eleven or twelve years. Thus a condition of resistance seems to begin to develop about the age of puberty. But the period of greatest incidence of new cases during the first few years of school life is worthy of emphasis. Is it the result of intimate contact like that

seen in measles, or is it due to an age-linked hypersensitiveness? The experience of many observers teaches that the infection is progressing steadily in the hearts of many children while avoiding other organs. For example, Sutton²³ found in the Bellevue Hospital 18 per cent of 427 rheumatic children to have well-developed rheumatic carditis without a previous history of either polyarthritis or chorea.

An apparent precursory factor in a majority of cases is repeated infection in the respiratory tract, often in the form of tonsillitis, sinusitis, middle ear disease, or bronchitis. In our experience so frequent has been the occurrence of acute tonsillitis within from one to five weeks of an acute attack that we now date the duration of a given attack from the onset of tonsillitis. But more detailed investigation of the previous state of health of patients usually reveals an earlier history of repeated sore throats, otitis media, or of recurring or almost continuous sinusitis. Not infrequently closer questioning discloses mild joint or growing pains with these upper respiratory infections. Coates and Thomas,²⁴ Coates and Coombs,²⁵ and Vining,²⁶ all report the finding of small subcutaneous granules in a fairly high percentage of school children. Whether or not these are genuine rheumatic subcutaneous nodules is a moot point; but their alleged demonstration by serious students of the disease should stimulate renewed investigation, because extensive painless nodules have been frequently observed in children having no other symptoms of sufficient severity to incapacitate them.

Other conditions in many children preliminary to an acute attack are loss of weight, anorexia, and general signs of mild intoxication. To these Vining has applied the term "toxic debility," and found that many of his rheumatic youngsters had in addition a history of intestinal disturbance of sufficient severity to point to the intestinal tract as an area whence the infectious agent might be spread throughout the body. The greater liability of children of the poorer classes to suffer disorders of malnutrition or to be deprived of certain accessory food substances suggests that possibly these are elements leading to a higher incidence of the disease among such individuals compared with people living on a higher economic scale. Recent studies of rheumatic children in out-patient departments furnish additional support concerning the influence of nutrition, in that loss of weight has been found to be one of the most common precursors of a relapse.

Recurrences of symptoms sufficiently severe to be called true relapses are commonly observed in children year after year; but symptoms and signs too mild to attract much attention not infrequently occur between relapses. For example, Shapiro²⁷ has recently noted electrocardiographic evidence of active cardiac damage in at least 60 per cent of 119 school children following apparently complete recovery from an acute attack; and Levy and Turner²⁸ have recorded electrocardiographic abnormalities weeks and months before the onset of acute symp-

toms. Persistent low-grade leucocytosis, unexplained on grounds other than that of persisting rheumatic infection, is not infrequent. Several of our patients have observed recurring erythema marginatum for months without appreciating its significance until more incapacitating manifestations forced them to seek hospital care, and the continuance of this peculiar rash for weeks or months following subsidence of acute arthritis not infrequently is an index of continuing infection.

Not only are such pictures seen in children, in whom we have learned to expect repeated relapses, but a similar history is not rare in adults when sought with sufficient care. For example, a man, aged thirty-three years, in good circumstances gave a history of acute tonsillitis in 1929 followed by acute rheumatic polyarthritis, then by tonsillectomy. In the winter of 1930 he had sore throat followed by a similar polyarthritis. But more careful questioning revealed repeated pharyngitis for eight to ten years previously, several attacks of sinusitis and recurring pain in the neck and back of sufficient severity to make movements difficult. It does not appear unreasonable to suppose that during the previous years he was suffering from mild rheumatic infection which was not brought to acute intensity until his first attack of severe tonsillitis. Such histories are not rare.

That tonsillitis plays an important rôle in precipitating many acute attacks of rheumatic fever we can accept as fairly well established. Where both diseases are reportable, the peak of the curve of the former antedates that of the latter by about two weeks. Glover,²⁹ in presenting details concerning several concomitant epidemics of these two conditions, advances the theory that they are spread by droplet infection which must reach a certain intensity before the resulting diseases reach epidemic proportions. In one outbreak carefully studied, the carrier rate for meningococci and the incidence of cerebrospinal meningitis and of rheumatic fever ran parallel; and this suggests that similar influences were at play in causing an increase in all three conditions. With a diminution in crowding there was a disappearance of both diseases, and with renewed crowding there was a return of an equal number of each. While these appeared to be primary attacks of rheumatic fever, one would like information concerning the previous history of the rheumatic individuals. Such questions are raised by the study of epidemics among children with rheumatic heart disease or convalescent from rheumatic fever, such as reported by Boas and Schwartz,³⁰ and Hiller and Graef.³¹ In the first epidemic reported by the former group there were four cases of bronchopneumonia accompanied by rheumatic carditis and one case of acute tonsillitis; in the second, although the precursory respiratory infection was not so marked, still acute rheumatic exacerbations developed in six boys in rapid succession. Among 19 nonrheumatic children in the same wards, none suffered from rheumatic fever, while in 22 previously rheumatic sub-

jects 11 developed acute rheumatic fever. In the epidemic reported by Hiller and Grace there were 43 children exposed, of whom 39 probably were previously rheumatic. Within five days of arrival at the camp there were twelve cases of upper respiratory infection, and within five weeks ten cases of polyarthrits, one of chorea, two of bronchopneumonia, one of acute bronchitis, and one of tonsillitis, pericarditis and pneumonia. Unfortunately the exact relationship of the upper respiratory infections to polyarthrits in each case was not recorded; nevertheless the high incidence of acute exacerbations of the disease in previously rheumatic children is worthy of emphasis, as is also the occurrence of severe pulmonary infection.

Scarlet fever is another disease intimately associated both with first attacks and with relapses of rheumatic fever. Some clinicians state that this disease in previously rheumatic children is practically always followed by acute manifestations of rheumatic fever. This suggests the possibility of comparable influences in all of the above mentioned epidemics, namely upper respiratory infection.

I realize fully the possibility of at least two interpretations of the phenomena described: (1) That rheumatic fever may be due to an unknown virus which may long lie latent in the body, and be incited to renewed activity because of the depressing influence of the acute respiratory infection; (2) on the other hand, it is possible that repeated and persisting low-grade infections induce or are accompanied by tissue changes too mild to be dignified by the name rheumatic fever, and that only with a stormy acute infection such as tonsillitis, or with invasion of the pulmonary tract by streptococci are the accompanying morbid processes raised above the clinical horizon. In either case the conditions existing prior to the attack of acute rheumatic fever are worthy of more detailed study than they usually receive.

To illustrate this point let us consider another group in which a contagious element may exist—the family. Since St. Lawrence's²² report eight years ago showing the incidence of multiple cases of rheumatic fever in a group of families to be as high as that of tuberculosis, there have been several confirmatory studies. It now appears that in a rheumatic family with one case the probability of occurrence of a second case is three or four times as great as in a family previously free from the disease. Although the various factors favoring the development of rheumatic fever may be almost as difficult of analysis within a family as in any other group, the family as a unit offers a promising field for investigation. For example, several years ago we learned that the mother of one of our rheumatic children frequently had sore throats within a short time of the appearance of relapses in the child. Following the removal of badly diseased tonsils in the mother her sore throat ceased, and since then the child has been free from

recurrences. Last winter a boy was admitted to the hospital with the following recent history of acute infections in himself, his mother, and sister:

First day, onset of grippe in patient and sister.

Second day, patient better; sister developed rash.

Eighth day, mother developed grippe with severe pain in back; sister recovered and lost rash.

Twelfth day, mother recovered.

Fourteenth day, patient developed fever and beginning polyarthritis.

Sixteenth day, patient had evidence of severe myocarditis.

Nineteenth day, patient had signs of pericarditis.

Such a history of contagion reminds one of the concomitant respiratory infections in the epidemics mentioned above and suggests the possibility of atypical nondiagnostic manifestations in the sister and mother. Indeed, a correlation of all of the illnesses of the members of fifteen rheumatic families by Paul and Salinger³³ has already yielded important data along these lines. They have shown that both primary and secondary attacks of rheumatic fever in certain members of a family have been accompanied by the simultaneous appearance of recognizable rheumatic fever in other members of the family, and not infrequently by the appearance of such nonspecific affections as sore throat, bronchitis, bronchopneumonia and skin rashes. They found in addition that the disease spread more frequently to the children under twelve years of age than to the older children and adults. Another striking feature among these families was the frequency with which so-called nonspecific respiratory infections occurred before the appearance of characteristic rheumatic fever. If an extension of this type of investigation yields similar data, we shall be in a position to formulate preventive measures not heretofore applied. Indeed, the information already available from the several reports above reviewed together with those of Andrien,³⁴ Grenet,³⁵ Irvine-Jones³⁶ and others suggests strongly the communicable nature of the infection. The time when health authorities will recognize this feature of the disease and attempt to assemble data compiled from compulsory notification may be nearer than we can now foresee. The numerical and economic importance of the problem far outweighs that of poliomyelitis, encephalitis, leprosy, and many other reportable diseases.

One more feature deserves attention: the hypersensitiveness of patients with rheumatic fever to streptococcal products, which has been found by most observers to be higher than in any other disease. One must admit that such hypersensitiveness is found in many nonrheumatic persons; hence these skin tests have not diagnostic specificity. But it has offered a possible explanation of certain peculiarities of the disease.³⁷ Mackenzie and Hanger,³⁸ Kaiser³⁹ and Ando⁴⁰ have all shown this type of hypersensitiveness to be rare or absent in infancy and to

increase in relative frequency with each half decade up to the period of adult life. In Duckett Jones's⁴¹ experience over 95 per cent of rheumatic children gave positive reactions to a filtrate of a single strain of indifferent streptococci. Derick and Fulton⁴² have recently found skin hypersensitivity to hemolytic streptococcal nucleoproteins in 88 per cent of rheumatic children between six and ten years of age compared with only 12 per cent in nonrheumatic children, surely a most significant difference, when it is noted that 88 per cent of their entire group of rheumatic fever patients gave positive reactions. It thus seems that hypersensitiveness to streptococci which appears with advancing years in many individuals occurs much earlier in rheumatic fever patients. Probably the repeated respiratory infections already so frequently mentioned are factors in conditioning a high sensitivity to streptococci; and it does not seem improbable that the condition recognized as acute rheumatic fever is incited by intense, focal infections such as acute tonsillitis, or otitis media—both due to hemolytic streptococci—occurring in already somewhat hypersensitive bodies. On the other hand, it must be recognized that we do not know definitely whether the relationship between streptococcal hypersensitiveness and rheumatic fever is causal or merely concomitant. Its existence, however, gives us a definite point of attack,⁴³ for could we influence it in one direction or another we would have an index with which to judge the effect of certain therapeutic efforts.

SUMMARY

Rheumatic fever is one of the most important of diseases economically, not only because of its acute manifestations, but also because of its rôle in the production of between 30 and 40 per cent of chronic cardiac disease in the latitude of the North Atlantic States. Microscopic findings indicate it to be a widespread disease involving by preference mesenchymal structures or mesenchymal portions of parenchymatous organs. Physiological stress and strain appear to favor localization of its manifestations, although it may be locally active without giving rise to symptoms; and various vulnerable organs may be either simultaneously or independently involved.

A number of factors appear to have causative relationships. Climatic conditions such as exist in temperate zones in winter favor its development; while sunny dry summers and tropical weather inhibit or prevent its evolution. Among the poorer classes it is from fifteen to twenty times more prevalent than in persons better housed and fed. Malnutrition and mild toxic states are frequent precursors of characteristic attacks. Most patients, both children and adults, give a history of repeated nonspecific infections of the respiratory tract, tonsils, sinuses, or middle ear, extending over several years, before a typical attack of rheumatic fever is ushered in by a severe focal infection.

Persons in intimate contact with patients during acute outbursts of rheumatic fever not infrequently suffer simultaneously from upper respiratory infections, or from typical rheumatic fever; hence there seems to be a distinct communicable factor favoring its spread. Because chronicity and relapses are so frequent, and crippling cardiac damage is of such gradual evolution, and finally because laboratory tests often reveal activity in periods between attacks, it seems justifiable to consider the infection to be characterized by long periods of preparation or sensitization of the tissues, the result of repeated mild infection before a more intense focal infection sets off the violent explosion recognized as acute rheumatic fever. Similar mild infections, moreover, apparently favor the continuation of true rheumatic activity in viscera already involved. It seems logical, therefore, to regard these preparatory periods and mild chronic infections between acute outbreaks as essential parts of the morbid process; hence our therapeutic and prophylactic efforts should be directed against them as well as against the more acute manifestations of the disease.

Note at time of correction of proof: While this article was in press the monograph⁴⁴ of Coburn appeared which presents much valuable additional evidence concerning the chronic and contagious nature of rheumatic fever; its geographic distribution; the high degree of cutaneous sensitivity of rheumatic fever patients to hemolytic streptococcal nucleoprotein; and finally a striking parallelism between an increase of hemolytic streptococci in the upper respiratory tract and relapses in patients with the disease. He apparently wishes to designate the malady as the "rheumatic state" and only recognizes "rheumatic fever" when it is diagnostically clear cut.

REFERENCES

1. Gräff, S.: Deutsche med. Wchnschr. 53: 708, 1927.
2. Fahr, T.: Klin. Wchnschr. 8: 1995, 1929.
3. Ehrström, R., and Wahlberg, J.: Acta med. Scandinav. 58: 350, 1923.
4. Wyckoff, J., and Lingg, C.: AM. HEART J. 1: 446, 1926.
5. Swift, H. F.: J. Exper. Med. 39: 497, 1924.
6. Gräff, S.: Rheuma Probleme. I. Ärzte Kursus des Rheuma-Forschungs-Instituts am Landesbad, 1928, p. 45, George Thieme, Leipzig.
7. MacCallum, W. G.: Bull. Johns Hopkins Hosp. 35: 329, 1924.
8. Gross, L.: Demonstration at Graduate Fortnight, New York Academy of Medicine, 1930.
- 8a. Von Glahn, W. C.: Am. J. Path. 2: 1, 1926.
9. Von Glahn, W. C., and Pappenheimer, A. M.: Am. J. Path. 2: 235, 1926.
10. Holsti, O.: Arb. a.d. Path. Inst. zu Helsingfors 5: 110, 1927.
11. MacLachlan, W. W. G., and Richey, De W. G.: Ann. Int. Med. 1: 506, 1928.
12. Gräff, S.: Deutsche med. Wchnschr. 56: 603, 1930.
13. Klinge, F.: Virch. Arch. f. path. Anat. 278: 438, 1930.
14. Hueck, W.: Beitr. z. path. Anat. u.z. allg. Path. 66: 330, 1920; 83: 152, 1929.
15. Paul, J. R.: Bull. Ayer Clin. Lab. 2, No. 12: 9, 1930.
16. Fahr, T.: Virch. Arch. f. path. Anat. 232: 134, 1921.
17. Evans, G.: Quart. J. Med. 14: 215, 1920.
18. Coombs, C. F.: Rheumatic Heart Disease, Bristol, 1924, John Wright & Sons.
19. Clarke, J. T.: J. Trop. Med. 33: 249, 1930.
20. Seegal, D., and Seegal, B. C.: J. A. M. A. 89: 11, 1927.
21. Houston, A. N.: M. Clin. North America 11: 1339, 1928.
22. Wilson, M. G., Lingg, C., and Croxford, G.: AM. HEART J. 4: 164, 1928.
23. Sutton, L. P.: AM. HEART J. 4: 145, 1928.

24. Coates, V., and Thomas, R. E.: *Lancet* 2: 326, 1925.
25. Coates, V., and Coombs, C. F.: *Arch. Dis. Childhood* 1: 183, 1926.
26. Vining, C. W.: *M. J. & Rec.* 128: 351, 395, and 453, 1928.
27. Shapiro, M. J.: *AM. HEART J.* 5: 504, 1930.
28. Levy, R. L., and Turner, K. B.: *Arch. Int. Med.* 43: 267, 1929.
29. Glover, J. A.: *Lancet* 1: 499, 1930.
30. Boas, E. P., and Schwartz, S. P.: *AM. HEART J.* 2: 375, 1927.
31. Hiller, R. L., and Graef, I.: *AM. HEART J.* 3: 271, 1928.
32. St. Lawrence, W.: *J. A. M. A.* 79: 2051, 1922.
33. Paul, J. R., and Sallinger, R.: *J. Clin. Investigation* 9: 10, 1930.
34. Andrieu, G.: *Le Rhumatisme Articulaire aigu Maladie contagieuse, Étude épidémiologique et Pathogénique. Recherches de Bactériologie* (privately printed), Toulouse, 1926.
35. Grenet, H.: *Gaz. d. hôp.* 93: 5, 1920.
36. Irvine-Jones, E. I. M.: *Am. J. Dis. Child.* 38: 659, 1929.
37. Swift, H. F., Derick, C. L., and Hitchcock, C. H.: *Tr. A. Am. Physicians* 43: 192, 1928.
38. Mackenzie, G. M., and Hanger, F. M.: *J. Immunol.* 13: 41, 1927.
39. Kaiser, A. D.: *J. Infect. Dis.* 42: 25, 1928.
40. Ando, K., and Ozaki, K.: *J. Immunol.* 18: 267, 1930.
41. Jones, T. Duckett: Personal communication, to be published in *Year Book Physicians Hospital, Plattsburgh, The William H. Miner Foundation, Plattsburgh, N. Y., 1930, vol. 2.*
42. Derick, C. L., and Fulton, M. N.: Personal communication, to be published.
43. Swift, H. F., Hitchcock, C. H., Derick, C. L., and McEwen, G.: *Am. J. M. Sc.* 181: 1, 1931; and *Tr. A. Am. Physicians* 45: 247, 1930.
44. Coburn, A. F.: *The Factor of Infection in the Rheumatic State*, Williams and Wilkins Co., Baltimore, 1931.

THE INTERPRETATION OF THE INITIAL DEFLECTIONS OF THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM*

FRANK N. WILSON, M.D., A. GARRARD MACLEOD, M.D., AND
PAUL S. BARKER, M.D., ANN ARBOR, MICH.

INTRODUCTION

BARKER, Macleod and Alexander¹ have recently reported a series of observations upon the exposed human heart which strongly suggests that the clinical electrocardiograms currently ascribed to right bundle-branch block are, in reality, due to left bundle-branch block and *vice versa*. This conclusion, if accepted, involves something more than a mere change in electrocardiographic nomenclature; it is in conflict with the prevailing views regarding the origin of the initial ventricular deflections of the normal electrocardiogram and of those curves now attributed to preponderant hypertrophy of the one or the other ventricle. These views, long held and almost universally accepted, were originally advanced by Lewis.² Based by him upon his careful and exhaustive study of the excitatory process in the vertebrate heart, they rest upon a foundation which has always seemed secure from both the experimental and the theoretical standpoint.

Nevertheless it seems to us impossible to reconcile these views with the observations upon the human heart referred to, and we therefore propose to reexamine the observations made by Lewis and his associates in order to determine whether they may justifiably be interpreted in such a manner as to avoid this conflict.

A FUNDAMENTAL HYPOTHESIS

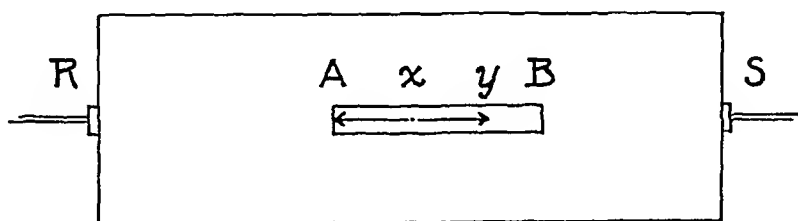
We may point out at the outset that we are in complete agreement with Lewis regarding the significance of the electrical axis, determined by means of Einthoven's triangle. We believe, as does he, that at any given instant this axis points in the direction in which, on the average, the excitatory process is at that moment spreading. In other words, the direction of the electric force produced by the excitation of any muscle unit is determined by the direction in which that unit is activated, and not at all, as was at one time thought, by its position in space with respect to the muscle mass, as a whole, of which it is a part.

This hypothesis was advanced by Lewis in order to explain his experimental results; it was discussed with Einthoven and accepted by him,³ and it is in accord with the results obtained by Craib⁴ in his experiments upon isolated strips of cardiac muscle. Recently, we have

*From the Department of Internal Medicine University of Michigan Medical School.

attention. Cardiologists have apparently avoided the dilemma by assuming, consciously or unconsciously, that the electric forces produced by the activation of the lateral wall of the right ventricle persist so long as this muscle remains in the active state, or at least until they are neutralized by the forces produced by the activation of the left ventricle. This method of avoiding the difficulty, however, involves the simultaneous acceptance of two theories which cannot be reconciled. It is impossible to hold that the electrical axis at any instant points in the direction in which, on the average, the excitatory process is spreading, and to believe at the same time that cardiac muscle continues to produce electric currents after it is fully active. The two theories which Lewis⁷ has called the "*theory of limited potential differences*" and the "*theory of distributed potential differences*" are incompatible with one another and cannot be successfully combined.

It is apparent, therefore, that the current interpretation of human branch-block curves is not entirely satisfactory. The difficulty which



$$Ax = xy$$

$$Rx = xS$$

Fig. 1.

we have referred to is fairly obvious. There are a number of others which are less easy to make evident. The nature of these difficulties and the manner in which they may be avoided can best be brought out by a discussion of some simple theoretical experiments.

ANALYSIS OF THE ELECTRICAL EFFECTS PRODUCED BY A MUSCLE STRIP

Let us suppose that AB (Fig. 1) is a short narrow strip of uninjured cardiac muscle immersed in a large quantity of Ringer's solution, and that two nonpolarizable electrodes, in contact with this solution at R and S , are attached to the right- and left-hand terminals of the string galvanometer respectively. If the muscle is stimulated at x , a point equidistant from R and S , the excitation process set up will spread to the right and to the left and will reach A and y , which are equidistant from x simultaneously. During this period the currents produced by the spread of the excitation process to the right (toward A) will be exactly neutralized by the currents produced by the spread of the excitation process to the left and the galvanometer string will remain

in the zero position. The currents produced by the activation of that part of the muscle lying between *y* and *B* will not, however, be opposed and will produce an upward deflection indicating relative negativity of *R*, with respect to *S*. During the inscription of this deflection the electrical axis will at all times point from the point of stimulation toward the center of the muscle. The absence of any deflection in the lead *RS*, during the period when the excitation process is spreading from *x* to *A* and to *y*, is dependent upon the assumption that *R* and *S* are equidistant from *x*. Suppose that instead of this indirect lead, a direct lead is employed in which the right-hand electrode at *R* is placed in contact with the end of the muscle at *A* and the left-hand electrode is allowed to remain at *S*. If *S* is distant from the muscle, the potential variations of the exploring electrode at *A* will be so much greater than those taking place at the electrode at *S* that the latter may be neglected. Inasmuch as the muscle units lying between *x* and *A* are much closer to the exploring electrode than the muscle units lying between *x* and *y* the activation of the former will have a much greater effect upon the potential of this electrode than the latter. Consequently, the electrode at *A* will be relatively positive with respect to the electrode at *S* and the galvanometer will record a downward deflection during the period in which the excitatory process is spreading from *x* to *A*. This downward deflection will reach its apex at the instant when the excitatory process reaches *A*; that is to say, at the moment when the muscle at *A* begins to pass into the active state. The electrode at *A* will remain positive with respect to the electrode at *S* until the muscle at *A* is fully active. The former electrode can never become relatively negative with respect to the latter except as a result of the activation of muscle units lying between *y* and *B*. The beginning of the upstroke, or "intrinsic deflection," recorded at *A* signals the arrival of the excitation process at *A*; the point where this upstroke crosses the base line marks approximately the completion of the activation of the muscle at *A*; the remainder of the upstroke is written by the activation of muscle units lying between *y* and *B*. The upward deflection in the indirect lead *RS* must begin at the instant when the intrinsic deflection of the direct lead has its onset, for it is at this moment that the currents produced by the spread of the excitatory process toward *A* begin to decline and become unequal to the opposed currents produced by the spread of the excitatory process toward *B*.

A CRITICISM OF THE CURRENT INTERPRETATION OF THE CANINE LEVOCARDIOGRAM

In the experimental studies carried out by Lewis and Rothschild⁸ the exploring electrode was placed upon the ventricular surface and the indifferent electrode upon the chest wall. The onset of the "intrinsic deflection" recorded in this manner must indicate that the excitatory

process, which travels from within outward, has reached the epicardial surface beneath the exploring electrode, and that the activation of the subjacent section of the ventricular wall has been completed, or at least that it will be completed within 0.01 second or less. The electrical effects produced by this portion of the ventricular wall must begin when the excitatory process starts to spread outward from the endocardial surface; they must end when it reaches the epicardial surface, or at any rate when the subepicardial muscle becomes fully active.

In discussing the discordant levocardiograms which he obtained in a small percentage of dogs, Lewis² stated that the direction of the electrical axis in the coronal plane was in agreement with representative readings, indicating the temporal orientation of the "intrinsic deflections" from the surface of the left ventricle with respect to R of Lead II. The figures which illustrate this statement² (Figs. 4 and 5, pp. 260 and 262) show, that about 0.01 second after "intrinsic deflections" are recorded over a given section of the free wall of the left ventricle, the electrical axis points in the direction in which this portion of the wall is activated. It is difficult to understand why the electrical axis should point in the direction in which the excitatory process spreads over a given mass of muscle at a time when the activation of this muscle has been practically, if not entirely, completed. There is still another difficulty. While the excitatory process is spreading through the lateral wall of the left ventricle, it must also be spreading through the septal wall, which is equally thick if not thicker. The electrical effects produced by the one group of fibers must be almost directly opposed by those which are produced by the activation of the other. There is little reason to suppose that these opposed electric forces differ materially in magnitude. It would seem, therefore, that the direction in which the lateral wall of the left ventricle is activated can hardly determine the position of the electrical axis until the activation of the septal muscle is complete. But when the excitatory process has completed its spread through the septum, activation of the right ventricle is already beginning and we are no longer dealing with purely left ventricular effects. The interpretation of the human dextrocardiogram and levocardiogram offered by Lewis² is open to the same objections.

The analysis of the experimental curves referred to is open to criticism on still other grounds. Surface readings taken from dogs in which the form of the levocardiogram was not investigated cannot justifiably be compared with the electrical axis calculated from a levocardiogram of the discordant type which is known to be exceptional.

We have pointed out that it is often difficult to form an accurate estimate of the average direction in which the excitation process is spreading at a given instant, even when the order of ventricular excitation is known. Consequently, as we have indicated in the discussion above, there is frequently an advantage in considering the direction of

spread, not at a given instant, but during a given period, or during the QRS-interval as a whole. There are, however, a number of considerations upon which an estimate of the kind first mentioned may be based.

ELECTRICAL EFFECTS PRODUCED BY A SPHERE OF EXCITABLE TISSUE

Suppose that the heart were a sphere of homogeneous excitable tissue and that the natural impulses were formed at its center. The excitation process would then spread radially outward as indicated in Fig. 2. Throughout the period of excitation the mass of fully active muscle must in that case form a perfect sphere completely enclosed by muscle in the resting state. Consequently, the imaginary surface separating active from resting muscle must also be spherical and must be com-

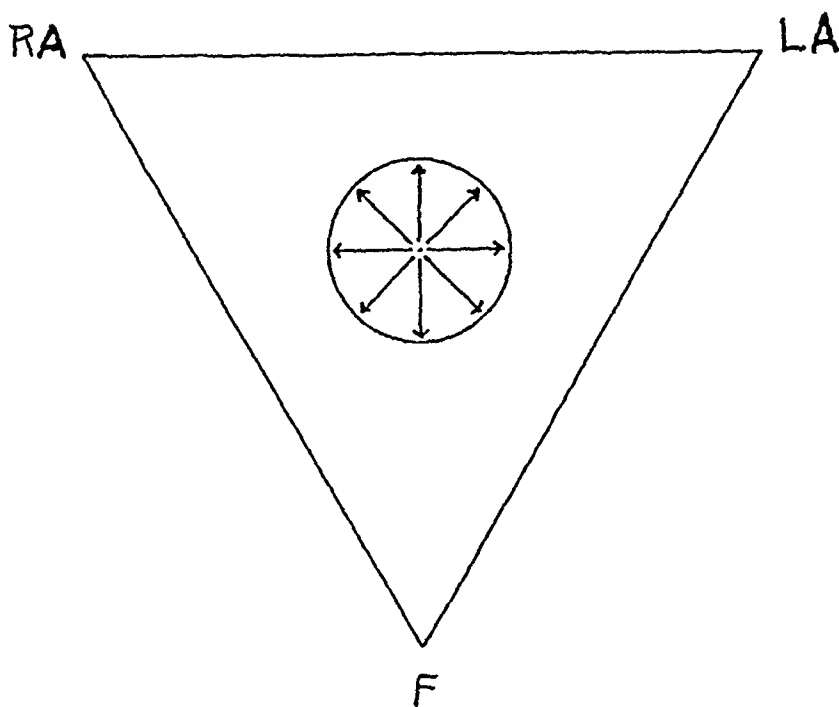


FIG. 2.

pletely closed. For every muscle unit undergoing activation in one direction at a given instant there must be another muscle unit undergoing activation in exactly the opposite direction; and the electrical effects produced by the one must be completely neutralized by the effects produced by the other. At no time could unbalanced or unopposed forces exist, and at no time could there be a deflection in any of the three standard leads.

Suppose, however, that this theoretical heart be stimulated artificially at some point between the center and the outer surface. The active mass of muscle and the surface separating it from inactive muscle must clearly be spherical until the excitation process reaches the surface at the point nearest the point of stimulation. No unbalanced forces and no deflections in any standard lead can occur previous to this time. As

soon as the excitation process reaches the surface of the sphere, however, unbalanced forces must occur, and obviously the magnitude of these forces must depend upon the number of muscle units producing unopposed electrical effects, and consequently upon the area of the opening or break in the surface separating active from resting muscle. The muscle units "visible" through this opening from a distant point, supposing the active muscle to be transparent, the resting muscle opaque, have no opposition, at least in so far as effects parallel to the line of vision are concerned.

It is not difficult to see that the principles underlying these statements apply in simple cases, such as the one discussed, which possess a high degree of symmetry. It is less easy to see that they are applicable also to cases of a complicated kind.

A METHOD OF ESTIMATING THE RESULTANT ELECTRICAL FORCE

If it is agreed that the electric forces which accompany the excitation wave are at all times perpendicular to the wave front, that is to say, normal to the imaginary surface which separates the active from the resting muscle, the electric field produced by these forces must be of the same character as that produced by a membrane polarized in a direction normal to its surface. From the mathematical standpoint the problem of determining the distribution of the electric currents is exactly the same in both cases. Furthermore, if we accept the membrane theory, the electric field in the first case is in fact the electric field of the polarized membranes of the fibers undergoing activation.

We have discussed the nature of the electric field surrounding a membrane polarized in the manner specified in another place.⁵ We have shown that, when the medium in which the membrane lies is infinite in extent, the potential V of any point P within the field is determined by the following equation:

$$V = \phi \omega$$

where ϕ is a constant, which may be defined as the electrical moment per unit surface of the membrane, and ω is the solid angle subtended by the membrane at P . The solid angle is defined and measured by the area cut out upon a spherical surface of unit radius, inscribed about P , by the cone formed by drawing a line from P to every point upon the boundary of the membrane. It may, for convenience, be considered negative or positive according as an observer looking through this cone sees the negative or the positive side of the membrane, for the sign of V is determined by this test. The same equation must also define the electric field surrounding the surface which separates active from resting muscle, the side of this surface adjacent to the resting muscle being considered positive and that adjacent to the active muscle, negative. The potential at any point within this field is therefore proportional to the

solid angle subtended by this surface at that point. It is true that if the medium is not infinite the equation given is not accurate; but, as we have pointed out elsewhere the error introduced by considering the body as if it were an infinite medium is for many purposes of little consequence. The equilateral triangle of Einthoven, upon which the calculation of the electrical axis is based, is founded upon the assumption that the apices of the triangle are distant and equidistant from all parts of the heart.⁹ If this assumption is made, the potentials of the apices of the triangle appear in fact to be strictly proportional to the solid angles subtended by the surface referred to at these points,⁵ although in this case the constant ϕ may no longer be equal to the electrical moment per unit surface, but a multiple of it. The assumption that

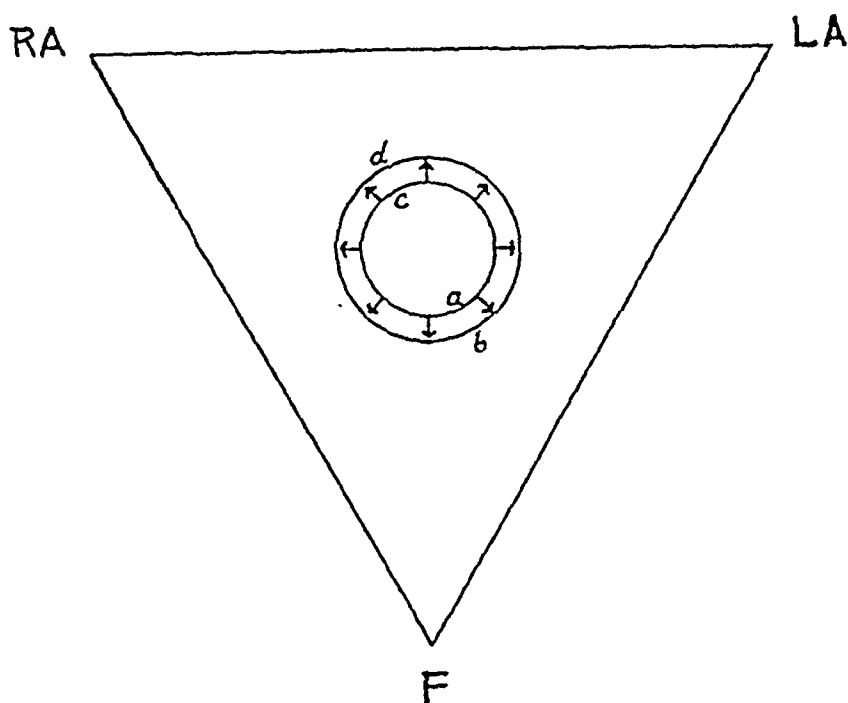


FIG. 3.

the apices of Einthoven's triangle are, for practical purposes, distant and equidistant from the heart is equivalent to the assumption that the heart is at the center of a spherical medium of large radius upon the surface of which the apices of the triangle lie. In that case the electrical axis may be defined as the vector drawn from the point on this spherical surface at which the solid angle subtended by the surface specified has its greatest negative to the point where it has its greatest positive value.

If the surface which separates active from resting muscle is completely closed, the solid angle subtended by it at all outside points must be zero. This is readily seen, for if such a surface is divided into two portions by means of an optional plane, the two surfaces thus formed will have the same edges or boundaries and the solid angles subtended

by them at any outside point must be equal in absolute magnitude, but unlike in sign. The sum of these two angles and consequently the potential of all points outside the surface under consideration must, therefore, be zero. So long as this surface remains closed no deflection can occur in any lead, direct or indirect. It is also clear that if there is a single opening in this surface, otherwise closed, the boundaries of the surface and of the opening are the same, and the solid angle subtended at any point by the one must be equal in absolute magnitude to the solid angle subtended by the other. If more than one opening is present, the sum of the solid angles subtended by all of them, each angle being given its proper sign, must be equal to the solid angle subtended by the surface. In estimating the potential at an outside point it does not matter, therefore, whether we consider the surface itself or the openings in it. Since the solid angle is determined by the boundaries of the surface alone, the configuration of the latter is immaterial.

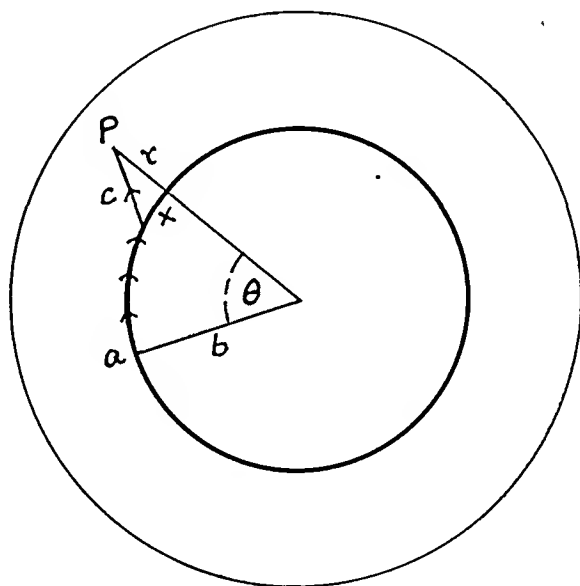


Fig. 4.

NORMAL AND TANGENTIAL COMPONENTS

Consider now a theoretical heart, which, instead of being a solid sphere, is a spherical shell of homogeneous excitable tissue, and suppose that all points on the inner surface of the shell are activated simultaneously. The excitation process will then spread through the wall along lines radiating outward from the center (Fig. 3), and again no deflections will occur, either in indirect or in direct leads, at any time during the period of excitation. We have assumed that all points on the inner surface of the shell are activated simultaneously; we can suppose that this result is brought about by a thin sub-endocardial layer of special tissue, which conducts the excitation process with infinite speed.

Suppose, however, that this thin layer conducts the excitation process with a speed which is only five times as great as the speed with which this process is transmitted by the tissues which enclose it. In that case the muscle units of the shell will not be activated in a direction normal to the surface. It is desirable to know the approximate direction in which these units will be activated. Let us suppose that the point of stimulation is a (Fig. 4); that b is the radius of the inner sphere and that P is any point of the shell, and r the distance of P from its inner surface. In reaching P the excitation process will obviously follow a course somewhat like that indicated by arrows; this course consists of two parts, $b\theta - x$ which represents the path through the lining layer, and c which represents the path through the ordinary tissue. Since the speed of transmission is five times as great along the first part of the path as the second the time t required by the excitation to reach P may be represented by the equation

$$t = \frac{b\theta - x}{5} + c$$

If the thickness of the shell is small in comparison with b , the angle subtended by the arc x must be small, and the triangular area bounded by r , c and x may be considered practically equivalent to a right triangle. Consequently c is approximately equal to $\sqrt{x^2 + r^2}$. Our equation then becomes

$$t = \frac{b\theta - x}{5} + \sqrt{x^2 + r^2}$$

Since the excitation process will reach P by the path which is least time-consuming we must determine the value of x when t reaches its minimum value. This may be done by differentiating t with respect to x and equating the derivative to zero. We have $\frac{dt}{dx} = -\frac{1}{5} + \frac{x}{\sqrt{x^2 + r^2}}$

and when $\frac{dt}{dx}$ becomes zero $x = \pm \frac{r}{\sqrt{24}}$. In other words x is approximately one-fifth of the distance of P from the inner surface of the shell. If the electrical force produced by the activation of any muscle unit of the shell is resolved into two components, one normal and the other tangential to the inner surface of the shell, the normal component will be approximately five times as great as the tangential.

ELECTRICAL EFFECTS PRODUCED BY A SIMPLE SHELL OF MUSCLE

Let us now return to the theoretical heart illustrated in Fig. 3. We have assumed that the inner surface of the shell is lined by a thin layer of special tissue which conducts the excitatory process five times as rapidly as the outer layers. The excitatory process set up by a stimulus applied at a will spread rapidly over the inner surface and slowly outward through the wall. The activation of each muscle unit will produce

an electric force which may be considered the vectorial sum of a normal and a tangential component, the former five times as great in magnitude as the latter. The electrical axis produced by the tangential components, considering these alone, will at all times point from the point of stimulation toward the center of the shell, or from *a* toward *d*, the point at which the excitatory process is ultimately extinguished.

The electrical axis produced by the normal components considered alone, will at first point from *a* toward *b*, or, from the center toward the point of stimulation. If we suppose that the relation between the thickness of the shell and the radius of its inner surface is such that the excitation process reaches *c* before it reaches *b* the electrical axis produced by these components will maintain this position until the excitation wave has reached the former point. During the latter part of the period of excitation the electrical axis will point from the point of stimulation toward the center, or toward *d* the point of extinction. In Lead II, which is parallel to the line *ac*, the normal components will therefore produce an upright followed by an inverted deflection and since the sum of all the normal components must be zero, if they all occurred at the same time, these deflections must be alike in amplitude and in duration; that is to say, one must be, in all respects, the inverse of the other.

Since the tangential components tend at all times to produce a deflection downward they must decrease the amplitude of the upward deflection and increase the amplitude of the downward deflection produced by the normal components. The actual curve recorded must therefore consist of a positive deflection followed by a larger negative deflection. If the stimulus be applied at *c* instead of at *a* the resulting curve must be in all respects reversed. If two stimuli be applied simultaneously, one at *a* and the other at *c* no deflections at all could occur in any of the three standard leads.

If, as we have assumed, the excitatory process reaches *c* before it reaches *b* there will be a short period during which the surface separating active and resting muscle is completely closed. During this period there will be no deflection in any lead; consequently the positive and negative waves will be separated by a short iso-electric period, which will begin when the excitation process reaches *c* and will end when it reaches *b*. If the thickness of the shell is gradually reduced this iso-electric period will become shorter; it will disappear when the thickness of the shell is reduced to a point which permits the excitation process to reach *c* and *b* simultaneously. A further reduction in the thickness of the shell will cause the end of the positive and the beginning of the negative deflection to fuse, algebraic summation taking place as the components responsible for these portions of the two curves become simultaneous.

ELECTRICAL EFFECTS PRODUCED BY A COMPLICATED SHELL

The simple conditions depicted in Fig. 3 may be made more complicated in a variety of ways. We may suppose, for instance, that the two spherical surfaces which bound the shell are eccentric so that in the neighborhood of a the wall is two or three times as thick as it is in the vicinity of c . It is clear that the normal and tangential components of the electrical forces produced by the activation of the thickest portion of the wall of such a shell, in comparison with those produced by the activation of the thinnest portion, will not be greater in magnitude at any given instant, but only in duration; and that the difference in this respect will be proportional to the difference in thickness. If all

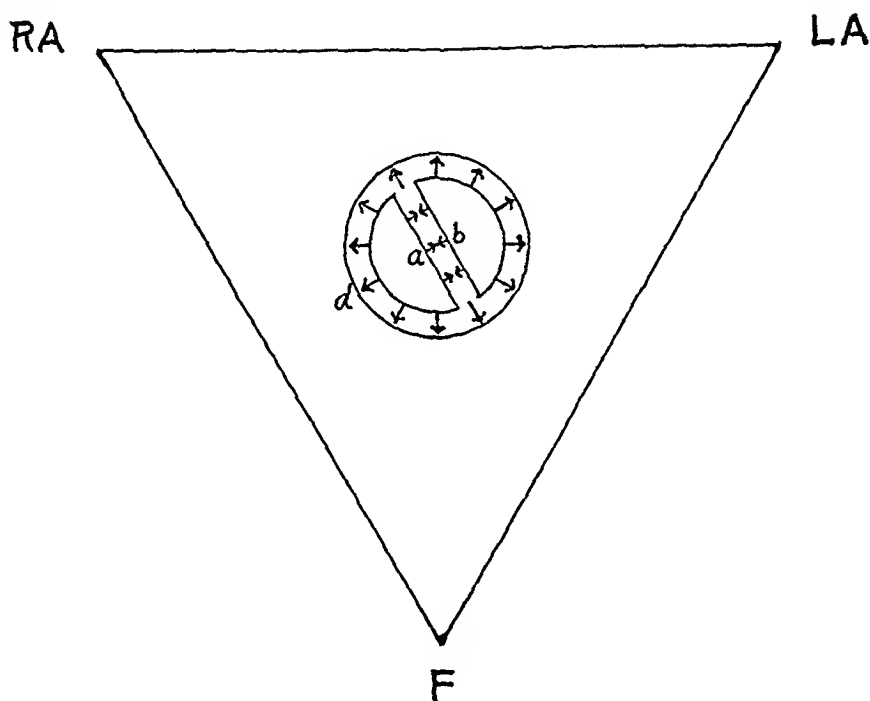


Fig. 5.

points on the inner surface are activated at the same instant there can be no deflection until the excitation process reaches the outer surface at the point where the wall is thinnest. It may be observed that the position and magnitude of the vector which represents the sum of all the tangential components is determined to a very large extent by the point of stimulation, whereas the vector which represents the sum of the normal components is determined by the distribution of the muscle of the shell wall. If the electrical forces produced are considered in their entirety, there is a close resemblance between the effect produced by shifting the point of stimulation in one direction and that produced by shifting the center of mass in the opposite direction.

We may also complicate the simple shell of Fig. 3 by introducing a septum as in Fig. 5. If all the points on the inner surface of this

double shell are activated at the same instant the course of the excitation process will be that indicated by arrows, and, since the electrical forces produced will be exactly balanced, there will be no deflection in any of the three standard leads during the period of excitation. If a stimulus is applied at *a* on the septal wall of the right ventricle of the shell, the electrical effect produced will be determined by the comparative thickness of the septum and the free wall of this chamber. If the excitation process arrives at *b* on the left side of the septum before it reaches *d* there will be a brief period during which the electrical axis points to the right and downward; but if the opposite is the case the electrical axis must at all times point to the left and upward. In either case, during the last half, approximately, of the period of excitation the electrical axis must point in the latter direction.

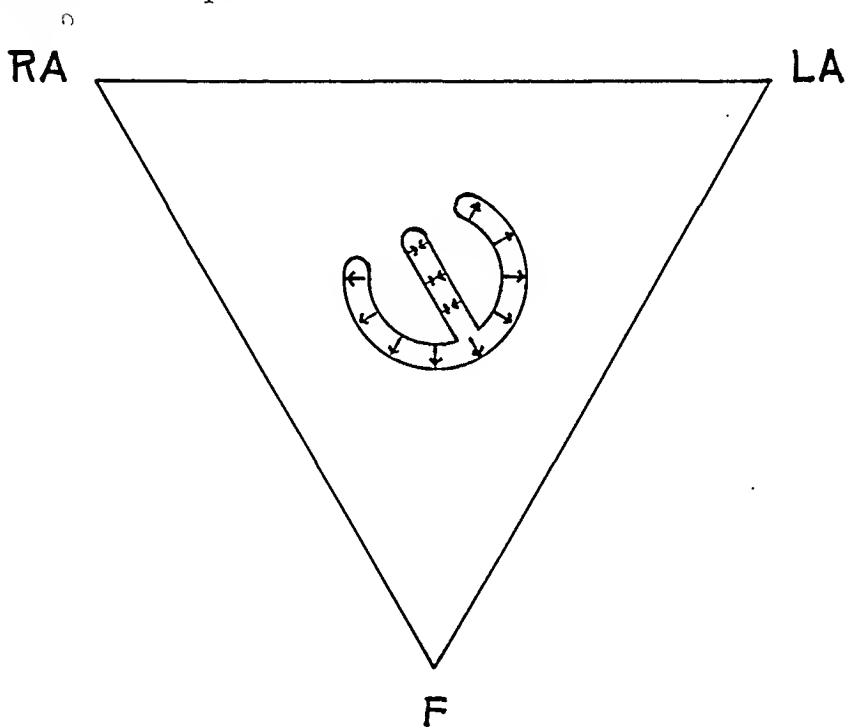


Fig. 6.

Finally, let us consider the theoretical conditions illustrated in Fig. 6. Here a cap has been removed from the shell so that the sum of all of the normal components is no longer zero. Consider that the general course of the excitation process over this structure is from within outward. If the excitation wave reaches all points on the inner surface before it reaches any point on the outer surface, there must be a period during which the solid angle subtended at any point by the surface which separates active from resting muscle is equivalent, or approximately equivalent, to that subtended at the same point by the openings in the shell at its base. It is clear that the solid angle subtended by these openings must be negative and large at *RA*, positive and large at *F*, and, as the figure has been drawn, positive and small at *LA*.

The electrical axis during the period referred to will, therefore, be nearly parallel to Lead II. If we draw a line from any apex of the triangle through every point upon the boundary of the surface which separates active and resting muscle, the potential of that apex at that moment is completely determined by the excitation of the muscle which lies within the cone or cones so formed. The sum of the effects produced by all other muscle is zero.

We have discussed these theoretical experiments and conditions at some length in order that the reader might have a clear understanding of the principles upon which, so we believe, the interpretation of the

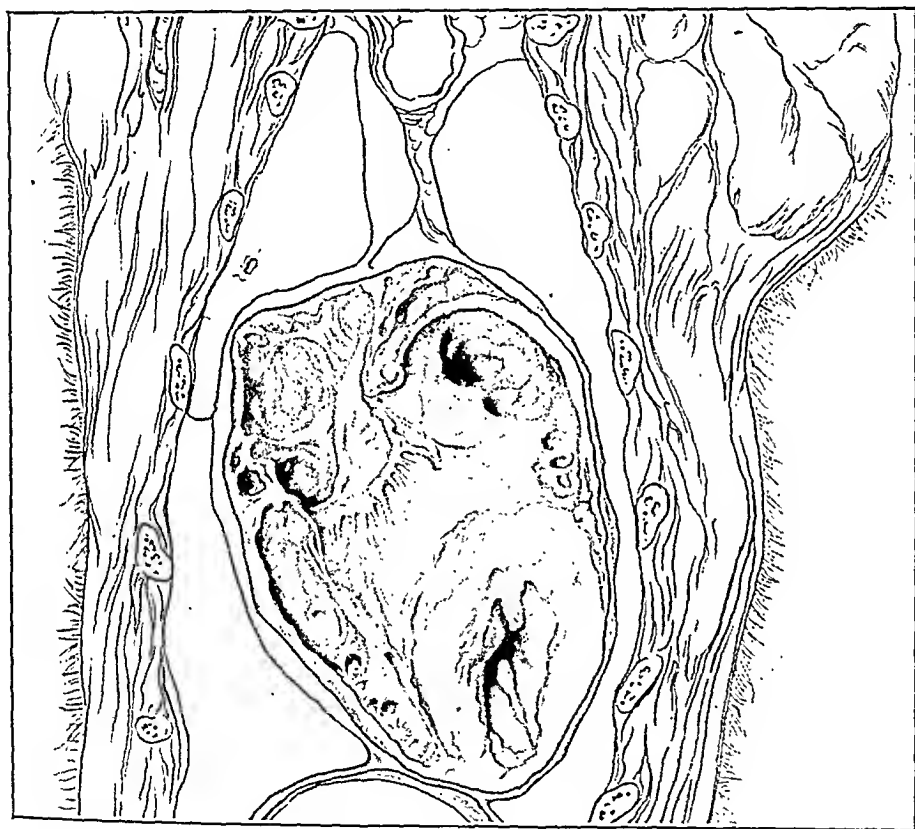


Fig. 7.—Frontal section of a dog's heart, well toward the ventral surface.

initial phases of the ventricular complex of the electrocardiogram must be based. We may now proceed to a consideration of the heart itself.

THE DEXTROCARDIOGRAM

We may first direct our attention to the right ventricle. Since the septum must obviously play a prominent rôle in determining the character of the dextrocardiogram, its position with respect to the three standard leads, and the direction in which it is activated are matters of importance. We have, therefore, prepared accurate drawings of the heart of the dog and of man sectioned in the frontal plane (Figs. 7, 8, 9, 10). Since the septum is not perpendicular to this plane, two

cuts were made in order to show the position of the more ventral (Figs. 7, 9) as well as of the more dorsal (Figs. 8, 10) portions of this structure. We may call attention here, to certain differences between the canine and the human heart.

In both dog and man the right ventricle lies on the right and ventral side of the left; in the former the right ventricle lies more above (Figs. 9, 10) the left (on its cephalic side); in the latter, more below it (Figs. 7, 8). As seen in coronal section the septum of the human heart is nearly parallel to that side of Einthoven's triangle which represents Lead II (Figs. 9, 10). The dorsal part of the dog's

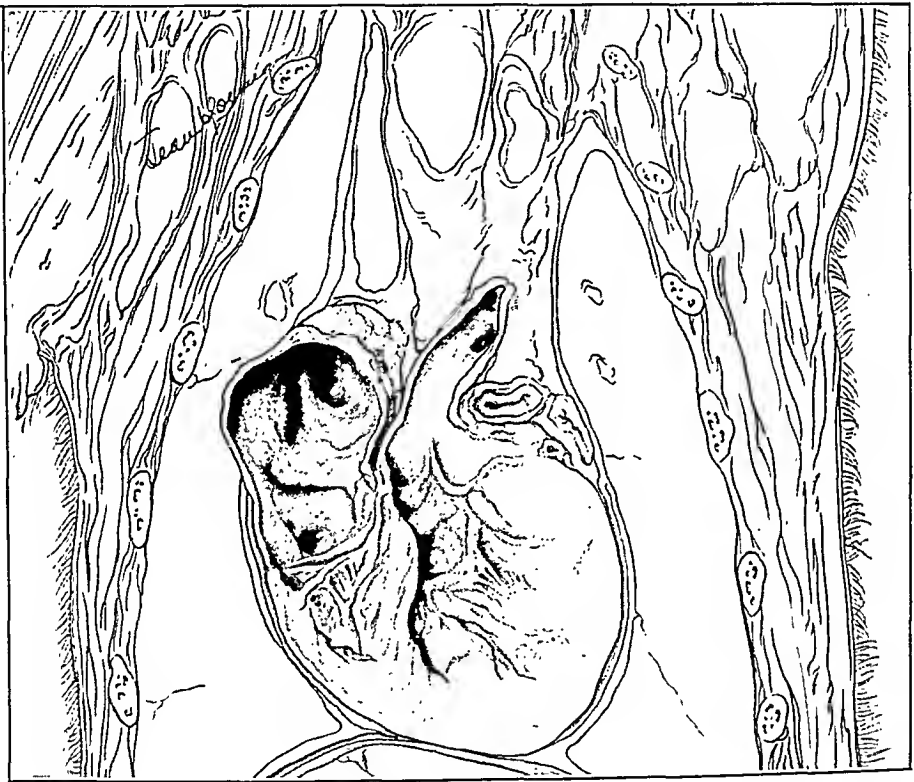


Fig. 8.—Frontal section of a dog's heart, more toward the dorsal surface.

septum is nearly vertical (Fig. 8); its ventral part is curved and may be described as convex upward and to the right (Fig. 7). The normal components produced by the activation of the septal wall of the right ventricle must tend to produce an electrical axis which in the dog points to the left and downward, in man to the left and upward. Our knowledge of the order in which the subendocardial muscle on the right side of the septum is activated is too meagre to permit an accurate estimate of the direction of the tangential components.

The observations of Lewis and Rothschild⁵ show that except for the conus region and the middle and upper portions of the septum, the entire endocardial surface of the dog's right ventricle is activated before the inscription of *R* in Lead II begins, or immediately thereafter.

Even at this time the excitation process has already reached the epicardial surface in the central region. In the imaginary surface which separates active and resting muscle there are at this period two openings; the electrical effects produced by those portions of the ventricular wall which lie opposite these openings, and these electrical effects alone, are unopposed. At the base of the ventricle, there is an opening in the surface which surrounds the tricuspid orifice and the canal of the conus arteriosus. As the excitation process spreads over the upper septum and over the endocardial surface of the conus, this opening may be divided into two parts. There is a second opening in the central



Fig. 9.—Frontal section of the human heart, well toward the ventral surface.

region, due to the arrival of the excitation process at the epicardial surface, which, although small at first, rapidly expands as the excitation process spreads over the outer surface of the lateral walls of the ventricle. The first opening must tend to produce an electrical axis pointing almost straight downward, perhaps slightly to the right at times; the second, an electrical axis pointing chiefly to the left, but with variations through a considerable angle. The resultant electrical axis must point downward and to the left. Apparently, the later and major portion of the canine dextrocardiogram must be attributed to electrical effects produced by the activation of the apical muscle and septal wall of the right ventricle. Except for the emphasis here laid upon the septal muscle, this view and that held by Lewis are not materially different.

The same principles may be applied to the interpretation of the human dextrocardiogram. We have pointed out that the position of the human heart with respect to the three standard leads differs materially from that of the dog. There is a further difference in the distribution of the subdivisions of the right branch of the His-bundle. Large and important strands of special tissue bridge the cavity of the dog's right ventricle. No similar conducting paths are found in man. It might be expected, therefore, that the excitation process would spread to the lateral wall of this chamber more quickly in the former than in the latter. The readings obtained by Barker, Macleod and Alexander¹ from the ventral surface of the exposed human heart are somewhat puzzling,



Fig. 10.—Frontal section of the human heart, more toward the posterior surface.

in that the earliest right ventricular points were not in the central region as in the dog but nearer to the base. These figures indicate, however, that the excitation process reaches the epicardial surface of the right ventricle somewhat later in man than in the dog. We need not attempt here to decide whether the cause of this difference is to be found in the distribution of the conducting tracts, the greater size of the heart, or in the thickness of the ventricular wall. It is clear that the excitation process spreads over the endocardial surface with great rapidity in man as in the dog. When the activation of the inner surface of the right ventricle has been completed, the surface which separates active from resting muscle must be open at the base. Because of the position of the human heart this opening will tend to produce an electrical axis which points downward and to the left in a direction

more or less perpendicular to the line of Lead III. When the excitation process reaches the epicardial surface, if it has not already done so, a second opening will appear on the lateral wall. Opposite this opening lies the septum producing electrical forces which, in terms of the electrical axis, point upward and to the left. As the opening increases in size, these effects will increase in magnitude. If we add these two vectors, the first pointing downward and to the left, the second upward and to the left, assuming that the latter, unlike the former, is small in the beginning but increases from instant to instant in magnitude, the resultant electrical axis will gradually rotate in a counter-clockwise direction.

We have pointed out that because it is difficult to estimate the average direction in which the excitation process is spreading at a given instant, there is an advantage in considering the average direction in which it spreads during the QRS-interval as a whole. Let us examine the effects produced by left branch block from this standpoint. The excitation process must spread through the septum from the right ventricle towards the left ventricle; it must spread over the left ventricle from its septal towards its lateral side; it must spread through the free wall of the left ventricle in the same general direction. Only the thin lateral wall of the right ventricle is activated in the opposite direction. In the dog the left ventricle lies on the left side of the right and below it and the average electrical axis, considering the period of excitation as a whole, must point to the left and downward. In man the left ventricle lies to the left of the right and above it, and the average electrical axis must point to the left and upward.

We believe that the clinical curves heretofore ascribed to right branch block are the result of left branch block, and consequently that the human curves which Lewis attributed to left ventricular effects and called levocardiograms were written by the muscle of the right ventricle and should have been labeled dextrocardiograms. We have indicated the manner in which, so we believe, the general outline of these curves and the counter-clockwise rotation of the electrical axis which takes place during their inscription are to be explained.

THE LEVOCARDIOGRAM

Lewis and Rothschild^s found it difficult to obtain reliable readings from the endocardial surface of the left ventricle. The figures which they give indicate that in the dog the apex and the septal wall are activated before the beginning of *R* in Lead II, and that some points on the upper septum are very early.

When the activation of the subendocardial muscle is completed, the surface which separates active from resting muscle must be open at the base where the ventricular wall is pierced by the mitral and aortic orifices. The forces produced by the apical muscle which lies opposite

these orifices are unopposed, and must tend to produce an electrical axis pointing almost straight downward. The left ventricular wall is thinnest at the apex and when the excitation process reaches the epicardial surface in this region a second opening will appear tending to produce an electrical axis pointing almost straight upward, or upward and to the right. The continued increase in the size of this opening as the excitation process reaches the epicardial surface over a larger and larger portion of the free wall must eventually enable it to more than overcome the effect of the opening at the base. The resultant electrical axis which at first points downward must therefore finally point upward and to the right.

In man because of the position of the heart, it would seem that the basal opening must tend to make the electrical axis point downward and to the left. As the activation of the lateral wall is completed septal forces pointing downward and to the right must become more and more effective. The resultant electrical axis must eventually point downward and to the right.

It may be pointed out that if the two vectors which represent the respective effects of the basal and the apical openings in the surface which separates active and resting muscle are directly or almost directly opposed to one another, the vector which represents their sum may suddenly undergo a reversal in direction if the relative magnitude of its components is gradually altered. If, on the other hand, the two vectors mentioned are not directly opposed the direction of the resultant will change more gradually; it will display a more or less uniform rotation.

Let us consider the direction in which the excitation process spreads over the ventricular muscle during the QRS-interval as a whole. In right branch block this process must spread through the septum from the left ventricle toward the right. The observations of Lewis and Rothschild show that it spreads over the right ventricle from its septal toward its lateral side. The free wall of the right ventricle must be activated in the same general direction.

Pointing in one direction we have the normal components of the electrical forces produced by the activation of the septum, and the tangential and normal components of the electric forces produced by the activation of the right ventricle. Pointing in the other direction we have only the effects produced by the lateral wall of the left ventricle. Clearly the mean electrical axis must point from the left ventricle towards the right. In the dog the right ventricle lies to the right of the left and above it, and the mean electrical axis should point to the right and upward. In man the right ventricle lies to the right of the left and below it, and the mean electrical axis should point to the right and downward.

We hope to return to this subject in a future communication in which we shall describe a method by means of which the mean electrical axis may be accurately calculated.

The foregoing considerations offer an explanation of the chief features of those human curves, which, according to our view, are produced by right branch block, and of the concordant levocardiograms which the majority of dogs display.

In a small percentage of dogs Lewis² obtained levocardiograms of the discordant type. During the inscription of these curves, which resemble the human curves now ascribed to right branch block, the electrical axis was found to rotate in a counter-clockwise direction. The views expressed by Lewis regarding the initial deflections of the human ventricular complex are based, to a very large extent, upon his interpretation of these discordant canine levocardiograms.

Lewis has tabulated^{2, p. 257} his measurements of the bicardiogram and levocardiogram of twelve dogs. Two methods of interrupting conduction through the right branch of the His-bundle were employed. In one-half of the experiments this structure was cut by means of a knife thrust through the ventricular wall just below the pulmonary valves. In the remaining experiments a clamp was employed. The right branch lies on the right side of the septum relatively close to the ventral wall of the heart. When one jaw of the clamp presses upon it, the other jaw pressing upon the left surface of the septum can hardly fail to injure some of those conducting tracts which constitute what is usually referred to as the anterior subdivision of the left branch of the His-bundle. Lewis² mentions this possibility, but points out that unless the damage to the left branch is very extensive the order in which the muscle of the left ventricle is activated, in so far as this may be determined from the form of the axial electrocardiogram, is not altered.

Subsequent observations have shown, however, that transection of the anterior subdivision of the left branch may alter the form of the initial deflections of the electrocardiogram materially. Rothberger and Winterberg¹⁰ found that when this structure was divided and the main stem of the right branch was also cut, the chief initial deflection of Lead I was usually upward. Wilson and Herrmann⁶ have also published curves from an animal in which a levocardiogram of the concordant type became discordant when the anterior subdivision of the left branch was injured.

It is noteworthy that in the only two experiments in which the curves obtained by Lewis were *strikingly* discordant a clamp was used.^{2, p. 257} In one of these curves *R* of Lead I reached a value of 2.6 millivolts (Dog H. V.), whereas *R* of the bicardiogram in the same lead measured only 1.3 millivolts. According to these figures the dextrocardiogram must show in Lead I a downward deflection of at least 1.3 millivolts

and must be of the discordant type. No one, so far as we know, has ever produced such a curve by cutting the left branch of the His-bundle.

We strongly suspect, therefore, that the discordant levocardiograms upon which Lewis lays so much stress, resulted from the use of a clamp which injured the anterior subdivision of the left branch of the His-bundle. We do not, of course, deny that in some animals, in which the deflections of Lead I are all comparatively small, the chief initial deflection in this lead is upward. Such curves cannot, however, be regarded as frankly discordant and do not resemble the human curves which are at present ascribed to right branch block.

Since the effects of cutting the anterior subdivision of the left branch upon the order of ventricular activation have not been studied it is not possible to offer a detailed explanation of the changes in the form of the levocardiogram which this procedure produces. It must be remembered that the plane of the septum is neither frontal nor sagittal but midway between the two. The conducting tracts which comprise the subdivision in question apparently distribute the excitation wave to the ventral portion of the septum and to the left anterior wall of the left ventricle, while the posterior division supplies the dorsal parts of the septum and the right posterior wall of this chamber. If the former tract is cut, the excitation process must spread from the dorsal margin of the septum toward the ventral margin, and consequently the tangential components of the electric forces produced by the activation of the septal muscle must point from right to left. The tangential components arising in the free wall must also be modified and must point in the same general direction. It is clear that whenever a conducting tract is blocked the amount or extent of spread, if we may use such an expression, toward the region which it supplies must be increased. It is not altogether surprising, therefore, that the levocardiogram is altered in the manner described. The chief difficulty arises in explaining why, during the last part of the *QRS*-interval when right ventricular effects should predominate, the electrical axis still maintains a right to left direction. It is hardly probable that the activation of that part of the left ventricular wall normally supplied by the anterior subdivision can be so greatly delayed as to permit it to play a prominent rôle in determining the position of the electrical axis at so late a period. It is possible, however, that because the dorsal part of the septum precedes the ventral part the excitation wave first reaches the right Purkinje system at a point much further to the right and much closer to the posterior wall than would otherwise be the case, and that the late right to left effects referred to are due to late activation of the conus. In the absence of more precise information than is now available it would be useless to speculate further.

It would seem that the effects produced by section of the posterior

subdivision of the left branch should be in a general way the reverse of those produced by cutting the anterior and this appears to be the case.

Before leaving this subject we should like to point out that it cannot be expected that section of the anterior subdivision will make the levocardiogram frankly discordant in all animals. It seems probable that it does so only in those dogs in which some tendency toward discordance is already present; possibly because of peculiarities of the conducting tracts of such a kind that the muscle supplied by the posterior subdivision of the left branch is activated earlier than in the average animal.

THE ORIGIN OF Q'

We must now turn to the earliest ventricular deflection of branch block curves; we refer to Q' . This wave is, on the whole, a more prominent feature of human than of canine curves. In the former it is almost always present; in the curves which we attribute to left branch block it is most prominent in Lead I and is absent in Lead III; in curves of the opposite type just the reverse is the case. In the dog's dextrocardiogram Q' is comparatively rare; when it occurs it is usually most prominent in Lead I, and absent in Lead III. In the levocardiogram it is common in Lead I; it is usually most prominent in this lead or in Lead II.

At first thought it seems obvious that Q' must be attributed to the excitation of the subendocardial muscle which is first to become active. To determine what region is first activated is, however, a matter of some difficulty. The excitation process spreads over the endocardial surface of the heart with great rapidity and even at the time when ventricular activity is just beginning many different points are passing into the active state at the same moment. Before the inscription of Q' is complete the excitation process has spread over a very large area.

Furthermore, endocardial readings are difficult to obtain and not entirely trustworthy. But even if the earliest point were known we could not be certain that Q' was written by effects which arose in the region in which this point lay. It is obvious that before an appreciable difference of potential can be recorded by indirect leads, a considerable mass of muscle must be involved. The rate at which the surface which separates active and resting muscle increases in a given region must depend upon the density of the Purkinje network, or rather the number of junctions per unit area between Purkinje and ordinary muscle fibers. It is quite possible that Q' is written not by the first region activated but by some region which is relatively early and which at the same time is activated with great rapidity. At the present time, therefore, any opinion as to the location of the muscle responsible for Q' must be based almost entirely upon the position of the electrical axis during its inscription.

If our conception of human branch-block curves is correct, Q' is probably not, if we may depend upon the criterion mentioned, of septal origin in man as Lewis apparently thought. It is difficult also to see how Q' of the canine dextrocardiogram can be due to septal effects; but Q' of the levocardiogram, on the other hand, may well be due to the activation of some region on the septal wall of the left ventricle. We have already referred to the curves published by Wilson and Herrmann⁶ to show the effect of cutting the anterior subdivision of the left branch upon the levocardiogram. It is interesting to note that these curves show a distinct Q' in Lead I after this subdivision was cut although none was present before. It is possible that further information regarding this deflection may be obtained from the form of the curves recorded by means of direct leads in animals and by means of precordial leads in man.

VENTRICULAR PREPONDERANCE

In connection with his analysis of the human dextrocardiogram and levocardiogram Lewis² also made a detailed study of the clinical curves which are attributed to preponderant hypertrophy of the left and of the right ventricle respectively. In left preponderance he found a counter-clockwise, in right preponderance a clockwise rotation of the electrical axis. He expressed the view that hypertrophy of a single ventricle increases the magnitude of its electrical effects and thus enables them to dominate the biocardiogram. This hypothesis offered a logical and convincing explanation of the resemblance between the curves attributed to enlargement of one ventricle and those attributed to branch block on the opposite side.

It must be remembered, however, that when the right or left ventricle is hypertrophied, the increase in muscle mass is not confined to the lateral wall of the chamber affected, but involves the septal wall as well. If the excitation process reaches the two ventricles at the same time, approximately one-half of the septal muscle, must be activated from each side.

Let us suppose that the left ventricle is greatly hypertrophied; the mass of the septum must then be greatly increased. Consequently, the electrical effects produced by the activation of the septal wall of the right ventricle, that is to say, by the right half of the septum, will be greatly augmented, without a corresponding alteration in the electrical effects, produced by the free wall, to which they are opposed. If the dextrocardiogram is, as we believe, normally dominated by septal effects, it will be exaggerated either in amplitude, in duration or in both.*

*The idea seems to be prevalent in the literature that if there was any relation between the mass of the heart muscle and the amplitude of the electrocardiogram, a small animal should display curves of lesser amplitude than a larger one. This idea is based upon a misconception; it fails to take into consideration the quantity of the conducting material in which the heart is immersed, and the mean distance of the electrodes from the heart. An infant's heart in a man's body would produce a very small curve.

The electrical effects produced by the septal wall of the left ventricle will also be magnified, but since the forces opposed to them must undergo an even greater amplification, the levocardiogram may actually be smaller than that of a left ventricle of normal size. According to this point of view hypertrophy of one ventricle enables the opposite chamber to dominate the ventricular complex.

It is possible, however, to look at the matter from another standpoint. If the septum is activated from the right and left sides in equal measure, the sum of the electrical effects produced by the septal muscle must be very small. Consequently, we may say that in left ventricular preponderance the ventricular complex is dominated by effects produced by the hypertrophied lateral wall of the left ventricle. This statement is not equivalent to the assertion that it is dominated by the levocardiogram, if we are correct in believing that the chief deflections of the latter are of septal origin.

We come, therefore, to the conclusion that left ventricular hypertrophy and left branch block have a similar effect upon the electrocardiogram, because both increase the number of muscle units or the total quantity of muscle that is activated from right to left. In one case the point of stimulation, so to speak, is shifted to the right; in the other the center of mass is shifted to the left.

This explanation of preponderance curves is incomplete in one respect. It does not account for the fact that Q' is most prominent in Lead I, in left preponderance, and most prominent in Lead III in right preponderance. It is difficult to understand how the relative mass of the two ventricles can determine the order in which the subendocardial muscle, which must be responsible for the deflection, is activated. For this reason, Barker, Macleod and Alexander¹ suggested that there must be a defect in conduction in the special tissues of the enlarged ventricle. It is very probable that many of the clinical curves which are attributed to preponderant hypertrophy of one or the other ventricle are partly, if not entirely, due to this cause.

As an explanation of all preponderance curves this hypothesis meets, however, with the objection that in the newborn right ventricular preponderance is a normal phenomenon and cannot therefore be due to a conduction defect in the right branch of the His-bundle, although it might conceivably be due to a greater length of the conducting tracts in the large right ventricle. In the infant's curve Q is most prominent in Lead III and is absent in Lead I, just as it is in the right ventricular preponderance of mitral stenosis and congenital pulmonary stenosis.

In the normal human electrocardiogram Q is almost never present in all three leads; it is either most prominent in Lead I or in Lead III. In the first case Q must be attributed to the activation of some region of subendocardial muscle in the left ventricle; in the second, to a similar mass of muscle in the right ventricle. The muscle concerned is probably

on the free wall near the apex in each instance. The order in which, or the relative speed with which, these two regions are activated determines whether Q shall occur in Lead I or in Lead III. In some manner, as yet obscure, the enlargement of one ventricle enables the other to write this deflection.

THE INITIAL DEFLECTIONS OF THE NORMAL VENTRICULAR COMPLEX

The initial deflections of the normal ventricular complex may be regarded as the algebraic sum of the corresponding deflections of the dextrocardiogram and levocardiogram. Each normal deflection may consequently be considered a right ventricular effect if it is contributed by the former, a left ventricular effect if it is contributed by the latter.

This method of analyzing the normal ventricular complex is entirely justifiable, but in some respects it is confusing. We discover, for instance, that although R of Lead I and R of Lead III record the same phenomenon, the former is written by one ventricle, the latter by the other. Let us consider R of Lead I in greater detail. Both ventricles are producing effects at the time when it is being written. The septal wall of the right ventricle is producing effects which point in the positive direction; we will call the sum of these effects $(+A)$. We may then represent the effects of the lateral wall of the right ventricle by $(-B)$, the effects of the septal wall of the left ventricle by $(-C)$, and the effects of the lateral wall of the left ventricle by $(+D)$. The right ventricular effects will then be represented by $(A - B)$, the left ventricular effects by $(D - C)$, the total effect by $(A - B - C + D)$.

Let us suppose that the septal effects of the two ventricles are equal in magnitude although opposite in direction. The total effect will then be represented by $(D - B)$. R is positive because D is greater in magnitude than B . Since D represents the effects of the lateral wall of the left ventricle, R may therefore be considered a left ventricular effect. But since the sum of the right ventricular effects $(A - B)$ is positive and the sum of the left ventricular effects $(D - C)$ is negative, R is contributed by the dextrocardiogram. It is therefore a right ventricular effect. Whether R of Lead I is considered a right or a left ventricular effect is therefore merely a matter of the point of view.

If the septal effects included in the dextrocardiogram and the septal effects included in the levocardiogram are equal in magnitude but unlike in sign, they must cancel when these two curves are added. Consequently, no material error is made by neglecting the septal effects, so long as the two sides of the septum are excited simultaneously. The interpretation of the initial deflections of the electrocardiogram advanced by Lewis neglects the normal components produced by the activation of the septal muscle almost entirely. This is not unjustifiable when the right and left bundle branches are conducting normally, and his interpretation of the initial deflections written by the normal and by the

hypertrophied heart are not in conflict with the views presented here, except in so far as the significance of *Q* is concerned. When, however, there is a defect in condition in either bundle branch, the effects produced by the septum cannot, according to our view, be neglected. In disregarding them under these circumstances we believe that Lewis was in error.

For the reasons indicated above, we regard the following interpretation of the normal initial deflections as equally accurate and more simple, than that which attempts to separate the effects produced by the two ventricles. *R* of the bicardiogram may be attributed to the fact that during the early phases of the period of excitation all of the electrical effects except those produced by the apical muscle which lies opposite the valvular orifices in the cardiac base are opposed by forces equal in magnitude and opposite in sign. *S* may be attributed to unopposed forces produced by the basal muscle of both ventricles after the apical portions of the cardiac wall have been completely activated. It is possible that some muscle in the upper septum and in the conus arteriosus which seems to be poorly supplied with Purkinje tissue may contribute to this deflection. The origin of *Q* has already been discussed.

COMMENTS

We have attempted to give a complete explanation of the initial deflections of the ventricular complex of the electrocardiogram, consistent with the observations upon the exposed human heart recently reported by Barker, Macleod, and Alexander.¹ This explanation is based upon the observations made some years ago by Lewis and Rothschild⁵ and by Lewis.² We have taken it for granted that these observations are correct in every particular. We have accepted without reservation the hypothesis advanced by Lewis that the electrical axis is determined by the average direction in which the excitation process is spreading. We believe, however, that some of the conclusions which Lewis drew from these observations are not well founded. We believe that he was misled by the histological studies of human branch block reported by Eppinger and Stoerk,¹¹ and by some observations upon the dog in which in attempting to place a clamp upon the right branch he injured conducting tracts on the left side of the septum.

We believe that the interpretation of the initial deflections of the electrocardiogram given in this article is sound in theory and correct so far as its major features are concerned. As regards minor details it must be considered tentative only. Many of the problems which we have attempted to solve are decidedly complicated and much desirable information bearing upon them is not available. In discussing problems of this kind from the theoretical standpoint it is necessary to make many simplifying assumptions; the magnitude of the errors thus introduced is difficult to estimate accurately. Furthermore, it is not

possible to be certain that all of the factors involved in the problems attacked have been correctly evaluated and that none have been overlooked.

CONCLUSIONS

The view advanced by Barker, Macleod, and Alexander, that the clinical electrocardiograms heretofore ascribed to right branch block are due to left branch block and *vice versa*, is not necessarily in conflict with the hypothesis that the electrical axis at a given instant points in the average direction in which the excitation process is spreading at that moment.

Both the dextrocardiogram and the levocardiogram, canine and human, are dominated by electrical effects produced by the ventricular septum.

Preponderant hypertrophy of one ventricle increases the magnitude of the electrical effects produced by the opposite ventricle by increasing the mass of its septal wall without altering its lateral wall.

NOTE.—We wish to thank Dr. H. B. Williams, and Dr. Kenneth Cole for a critical reading of the manuscript of this article before it was submitted for publication.

REFERENCES

1. Barker, P. S., Macleod, A. G., and Alexander, J.: AM. HEART J. 5: 720, 1930.
2. Lewis, T.: Phil. Trans. Roy. Soc. B, 207: 221, 1916.
3. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, ed. 3, 1925, Shaw and Sons.
4. Craib, W. H.: Heart 14: 71, 1927.
5. Wilson, F. N., Macleod, A. G., and Barker, P. S.: Unpublished.
6. Wilson, F. N., and Herrmann, G. R.: Heart 8: 229, 1921.
7. Lewis, T.: Arch. Int. Med. 30: 269, 1922.
8. Lewis, T., and Rothschild, M. A.: Phil. Trans. Roy. Soc. B., 206: 181, 1915.
9. Wilson, F. N.: AM. HEART J. 5: 599, 1930.
10. Rothberger, C. J., and Winterberg, H.: Ztschr. f. d. ges. exper. Med. 5: 264, 1917.
11. Eppinger, H., and Stoerk, O.: Ztschr. f. klin. Med. 70: 1, 1910.

PARAFFIN INFILTRATION OF HEARTS

A PERMANENT METHOD FOR PRESERVATION*

LOUIS GROSS, M.D., AND EUGENIE LESLIE, M.D.†
NEW YORK, N. Y.

INFILTRATION of organs with paraffin is a relatively old procedure, the general principle being to dehydrate the fixed organ and to infiltrate it with paraffin much as is done in the routine manner for blocking tissues. An organ thus treated has the following properties: (1) it is very easy to handle and is therefore excellent for teaching purposes; (2) the normal topographic relations of the organ are retained; (3) the tissues are permanently fit for histological studies.

Our purpose in writing this report is to describe in some detail a method of paraffinizing hearts which is simple and permits the retention of the original topographic relations in excellent condition. While the technic described is based on its application to the heart, it can be used with slight modification for other organs.

METHOD

The unopened heart is obtained as soon after death as possible and a description given. In order to examine the interior of the heart so that a macroscopic diagnosis may be immediately available, it has been our practice to use an electrically lighted nasal speculum, such as the Cameron Diagnostoscope with adjustable trigger Nasoscope Head. During this examination the larger masses of blood clot should be removed. Special glass cannulas are now tied into the aorta, pulmonary artery, superior vena cava and one of the pulmonary veins. The cannulas should be almost of the same size as the orifices into which they are tied and they should have a small sloping flange (Fig. 1). In order to block the other pulmonary vein orifices, the inferior vena cava and any other holes which may have been made in the auricles during the autopsy, wooden pulleys of various sizes‡ are used (Fig. 2). As in the case of the cannulas, the size of the pulleys should be as nearly as possible the size of the hole to be blocked up.

The pulley is placed into the hole and the auricular tissues are tied around the groove by means of a thread. The purpose of this procedure is to prevent the puckered appearance and collapse of the auricles

*From the Laboratories of The Mount Sinai Hospital, New York City.

†Aided by a grant from the Lucius N. Littauer Research Fund.

‡We find it convenient to use pulleys 1 cm. in width and 1, 2, 3, 4, 5 and 6 cm. respectively in diameter.

which results from merely tying the tissues together around the hole.

Short lengths of rubber tubing are attached to the pulmonary artery and aortic cannulas and are joined together by means of a glass "Y" tube. A hook is passed under the "Y" tube and the heart is in this way suspended from a stand (Fig. 3). Short lengths of rubber tubing are also attached to the cannulas inserted into the auricles, and these are individually suspended from the stand in such a manner that all pressure is taken off the auricles and no distortion of the auricular walls is produced. In other words, the cannulas should be so suspended that their main axis is parallel to the pulmonary vein and superior venâ cava respectively.

The suspended organ is lowered into a container of approximately three liters capacity. The apex of the heart should reach to about 3 cm. above the bottom of the container. A large tank containing neu-

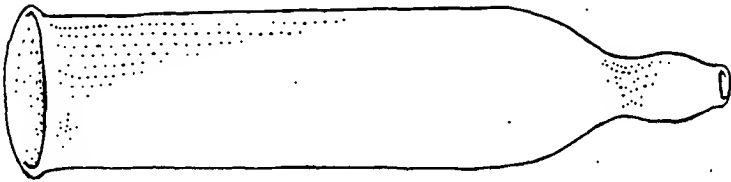


Fig. 1.—Type of glass cannula tied into aorta, pulmonary artery, superior vena cava and one of the pulmonary veins.

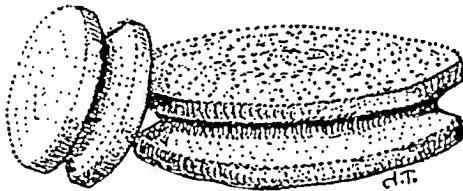


Fig. 2.—Type of wooden pulley used for blocking orifices in heart.

tralized formaldehyde sodium chloride solution* is placed on a shelf approximately 2 feet above the level of the apex of the heart. This is now attached to the "Y" tube and the formalin allowed to fill the chambers of the heart in this retrograde manner.

In most of the specimens the semilunar valves are sufficiently incompetent to allow the formalin to flow backward through the ventricular and auricular systems. In this way air is driven up the auricular cannulas, and as soon as the formalin appears the rubber tubes connected to these cannulas are clamped off. In those instances where the semilunar valves are competent it is necessary first to fill the auricular and ventricular systems through the auricular cannulas. When this is accomplished the auricular cannulas are tied off and perfusion is continued through the arterial cannulas. The shrinkage of the valves which takes place in the formalin generally eventually

*Solution of formaldehyde, U. S. P., 10 parts; 1 per cent sodium chloride solution. 90 parts. This solution is rendered neutral with a weak alkali.

accomplishes the desired result of allowing the fixing fluid to pass by the semilunar valves.

The heart having been set up and filled in the manner indicated, the container in which the heart hangs is now filled with formalin until it reaches above the level of all exposed tissue. Twenty-four hours later the formalin inside and outside the heart is replaced by fresh formalin. This is repeated for a third time twenty-four hours later.

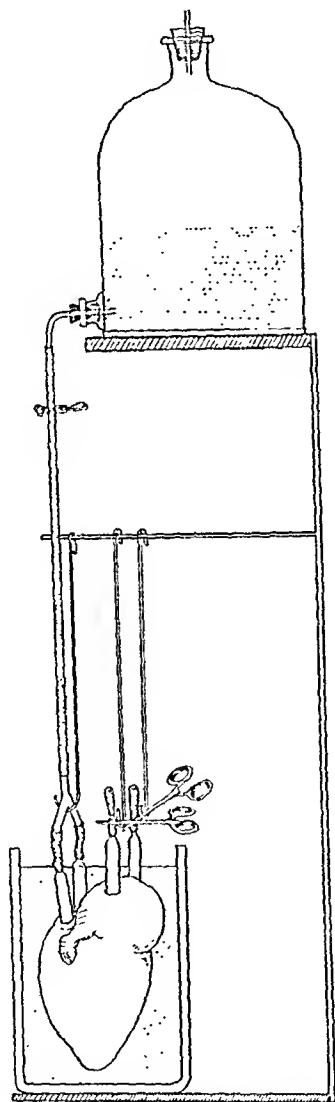


Fig. 3.—Method of suspending heart and perfusing with formalin.

If it is so desired, blocks of tissue may now be cut from the heart, although it is advisable to delay this as long as possible.

After complete fixation in this manner the cannulas are carefully removed, the wooden pulleys, however, being left in place. The heart is now gently dried with a towel and placed into a container holding approximately 2-2½ liters of 65 per cent alcohol. The heart should be placed on a bed of cotton and, depending on its size, should remain

in the container for approximately twenty-four to forty-eight hours. The organ is passed through increasing percentages of alcohol (80 per cent, 90 per cent, 95 per cent and absolute), again leaving it in each of these fluids for twenty-four to forty-eight hours. It is advisable to sponge the heart gently with a dry towel between these stages.

After the last procedure, measure the strength of the alcohol by means of an alcoholometer. If this measures less than 98 per cent, place into fresh absolute alcohol. After forty-eight hours test again. Continue these changes until the absolute alcohol remains at least 98

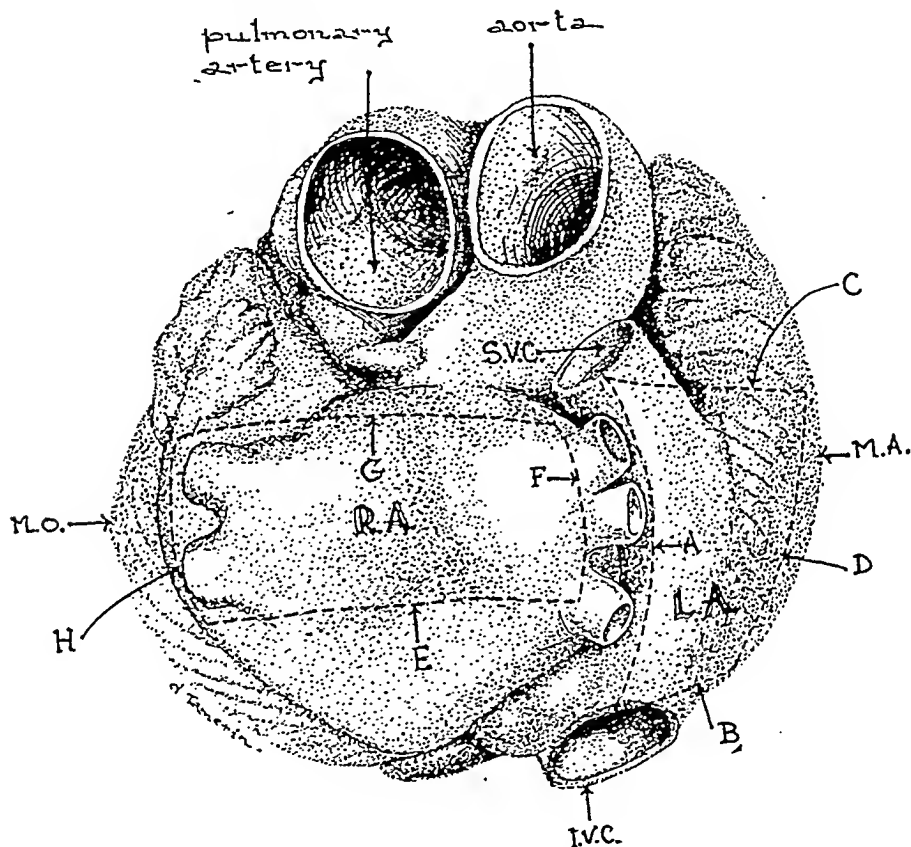


Fig. 4.—Method of opening auricles. I.V.C. = inferior vena cava. S.V.C. = superior vena cava. L.A. = left auricle. R.A. = right auricle. M.A. = margo acutus. M.O. = margo obtusus.

per cent. The last stage of dehydration from about 96 per cent alcohol can be expedited by placing the organ in fresh anhydrous acetone. We prefer absolute alcohol.

Place into toluol for forty-eight hours. Change into fresh toluol for twenty-four hours. Drain off the toluol rapidly and place into the following mixture kept in a paraffin oven at 56 degrees:

| | | |
|----------------------------------|----|--------------------|
| Paraffin, melting point 53-55 C. | -- | 95 parts by weight |
| Pure unbleached beeswax | -- | 5 parts by weight |

Keep in an incubator for twenty-four hours. Transfer to another paraffin-wax bath for twenty-four hours. Remove from bath, insert

a hook into the apex and suspend the organ upside down in order to allow the excess paraffin-wax to drain off.

While the heart is still slightly warm it should be opened in the following manner:

Insert a knife into the inferior vena cava, the edge pointing toward the anterior surface of the heart. Push the blade through the superior wall of the right auricle until the superior vena cava is reached, cutting as close to the interventricular septum as possible (Fig. 4 A). Reinsert the knife into the inferior vena cava with the edge pointing

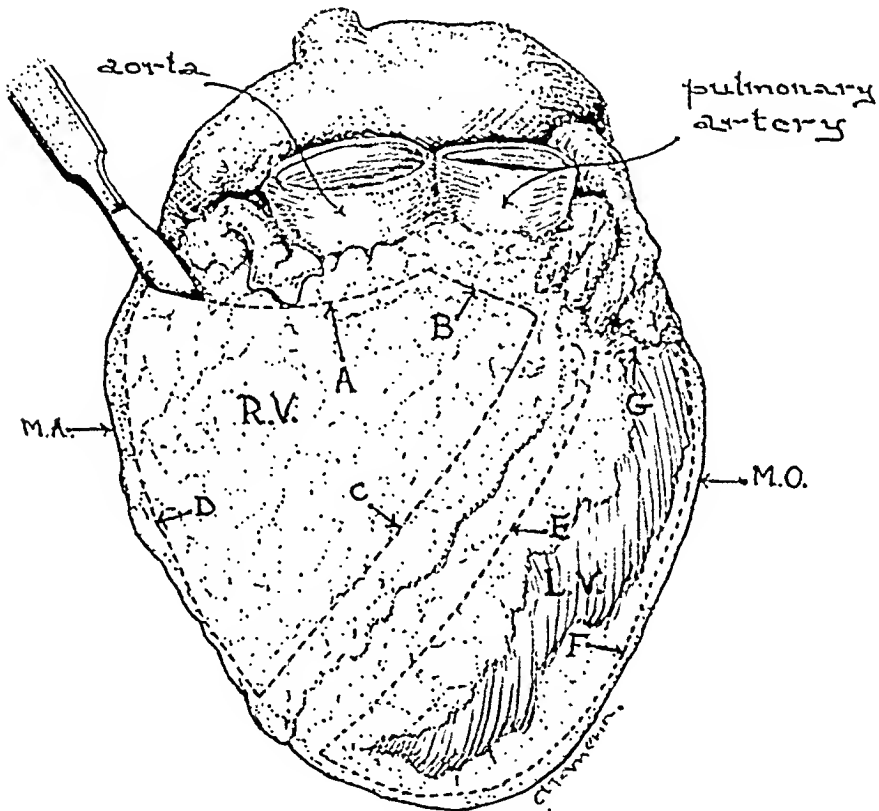


Fig. 5.—Method of opening ventricles. M.A. = margo aentus. M.O. = margo obtusus. L.V. = left ventricle. R.V. = right ventricle.

toward the margo aentus. Make an incision over the superior wall of the right auricle parallel to its posterior wall until the auriculo-ventricular sulcus is reached (Fig. 4 B).

Insert the knife into the superior vena cava with the edge pointing toward the margo aentus. Make an incision along an imaginary line which joins the superior vena cava with a point 5 mm. posterior to the junction of the inferior border of the right auricular appendix with the auriculo-ventricular sulcus (Fig. 4 C). Connect the distal point of this incision with the posterior auricular incision previously made (Fig. 4 D). In this manner the top of the right auricle is easily removed.

Trim the pulmonary artery to within a centimeter of the level of the valve commissures, and the aorta to any level desired. Insert the point of the knife slightly below the right auriculo-ventricular sulcus at the junction of the latter with the margo acutus. The edge of the knife should point toward the pulmonary artery, the blade being held in such a manner that the knife forms an angle of approximately 45 degrees with the upper segment of the main axis of the heart and 135 degrees with the lower segment (Fig. 5). Push the blade through the myocardium into the right ventricle being careful not to strike the delicate tricuspid valve. Carry the blade forward following the contour of the auriculo-ventricular sulcus until the incision reaches to within $\frac{1}{2}$ cm. of the lower border of the pulmonary cusps (Fig. 5 A). This can be seen by looking down the pulmonary orifice.

Turn the blade downward and continue this incision parallel with the plane of the pulmonary cusps until the interventricular septum is reached (Fig. 5 B). Now turn the blade edge down and carry the incision to the apex of the right ventricle, keeping the knife at all times close to the interventricular septum (Fig. 5 C). This incision can be easily watched through the pulmonary orifice.

Insert the blade of the knife into the margo acutus at the first point of the original ventricular incision, i.e., below the junction of the auriculo-ventricular sulcus and the margo acutus, and carry the incision down to join the last part of the interventricular cut (Fig. 5 D). While this incision is being made, look through the tricuspid orifice to make sure that the tricuspid valve is not injured. Gently raise this window of right ventricular myocardium. It will be found that the trabecula septomarginalis or the anterior papillary muscle makes it impossible to remove completely the myocardial segment. This connection is severed by the knife at a convenient site, and the right ventricular chamber is thus opened for inspection.

Insert the blade of the knife through one of the pulmonary veins (preferably the right posterior) with the edge pointing toward the margo obtusus (Fig. 4). Make an incision across the superior wall of the left auricle until the auriculo-ventricular sulcus is reached (Fig. 4 E). Starting with the first point of this incision turn the knife edge anteriorly and cut through the superior wall of the left auricle until a point is reached on the latter approximately opposite the superior vena cava of the right auricle (Fig. 4 F). Turn the edge of the knife toward the margo obtusus and make an incision along a line which runs to approximately 5 mm. posterior to the junction of the left auricular appendix with the auriculoventricular sulcus (Fig. 4 G). Complete the incision parallel to the line of the auriculo-ventricular sulcus (Fig. 4 H). This frees the left auricular window and thus an opening is made into the left auricle leaving enough of the posterior wall of the latter to show pathological lesions.

The last and most difficult incision remains. Insert the knife blade into the anterior wall of the left ventricle at a point approximately 1 cm. below the junction of the left coronary artery with the left anterior descending branch (Fig. 5). The cutting edge should point toward the inferior border of the interventricular septum. Watching the contour of the interventricular septum and estimating the thickness of the latter as closely as possible, make an incision parallel to the right interventricular incision (Fig. 5 *C*) with the object in mind of exposing as much left ventricle as possible without actually cutting into the interventricular septum (Fig. 5 *E*). The incision should be carried as far as the *margo acutus*.

Insert the knife at a point 1 cm. below the auriculo-ventricular sulcus at the latter's junction with the *margo obtusus* with the cutting edge pointing toward the apex of the heart. Look through the mitral valve orifice to make sure that the mitral cusp is not perforated by the point of the knife. With the blade penetrating through the entire thickness of the left ventricular wall carry the incision down to the apex of the heart and continue it around the apex until it joins the left interventricular incision described above (Fig. 5 *F*). Make a connecting incision between the upper ends of the interventricular and *margo obtusus* incision (Fig. 5 *G*).

If the tissue has been cleanly cut it will be found possible to raise slightly the lower border of this left ventricular flap. It will be impossible, however, to remove the flap because of the stout left anterior papillary muscle which binds it to the mitral flap. The papillary muscle is severed close to its apex by a knife, and the left ventricular flap is thus removed. Carefully clean out all blood clot.

If the opening of the heart is performed, as it should be, while the myocardium is slightly warm, it will be found very simple to remove whatever blocks are necessary for microscopic study. In order to examine the coronary arteries, however, it is desirable that coronal incisions of the vessels should be made during one of the dehydration stages in alcohol. Blocks can then be removed. If at some future occasion it is necessary to cut additional blocks from the heart, it should be placed in a 56 degree incubator for about fifteen or twenty minutes until the paraffin softens.

THE CARDIODYNAMIC EFFECTS OF ACUTE EXPERIMENTAL MITRAL STENOSIS*

LOUIS N. KATZ, M.D., AND MORTIMER L. SIEGEL, M.D.
CLEVELAND, OHIO

A DIFFERENCE of opinion exists in regard to the cardiodynamic effects of acute mitral stenosis, experimentally produced, except all are agreed that the left intra-auricular pressure is elevated. Invariably, acute mitral stenosis when produced in animals with intact circulation was found to elevate the pressure in the pulmonary artery (in severe stenosis, in the right ventricle also) and to lower the pressure in the left ventricle, systemic arteries and veins (Kornfeldt,¹⁶ 1892; Gerhardt,^{5, 9} 1901, 1912; MacCallum and McClure,¹⁷ 1906; Hirschfelder,¹⁰ 1908 and Dzwankowska,⁷ 1924). On the other hand, similar experiments made on the heart-lung preparation by Straub,¹⁹ 1917, showed only a transient fall in pressure in the left ventricle and systemic arteries, and a fall in the maximum pressure of the right ventricle accompanied by an unchanged initial pressure. The question arises whether the results of Straub indicate that the heart-lung preparation is unable to predict what happens in the animal when its circulation is intact, or, on the other hand, whether the graphic method used by the other investigators failed to depict the true state of affairs.

Mitral stenosis is perhaps the valvular defect most difficult to produce experimentally. Preliminary experiments soon convinced us that some of the discrepancy in previous results was caused by artefacts inherent in certain methods of producing mitral stenosis. In these preliminary trials several of the methods previously described were tested, e.g.: the suture method (MacCallum and McClure,¹⁷ 1906, Hirschfelder,¹⁰ 1908 and Allen,¹ 1924); invagination of the left auricle through the A-V ring; compression of the mitral ring manually or, as suggested by MacCallum,¹⁷ 1906, Cushing and Branch⁵ 1907, and Hirschfelder,¹⁰ 1908, by clamp or suture.† The artefacts were produced in three chief ways: (1) by clotting of blood, (2) by traction and (3) by compression of the coronary arteries.

Since the results of mitral stenosis can be influenced by these artefacts, a few words on the effects of these artefacts and on the ways in which they were avoided or discounted is given. Traction in producing the mitral stenosis may lead to an aortic stenosis also. This was found

*From the Department of Physiology, Western Reserve University Medical School, Cleveland, Ohio.

†Scarifying the valves by strong alkali, radium or microorganisms as suggested by Coryllos, Edwards and Bagg,⁴ 1923, and by Cutler, Levine and Beck,⁶ 1924, was not tried as it was not suited for our purposes. We felt that we could not produce a stenosis of sufficient degree with Straub's valve method.

to be the case when mitral stenosis was produced after an animal's death. In the living animal changes in the intraventricular and aortic pressure curves, which resemble those described in aortic stenosis by Katz, Ralli and Cheer¹³ (1928), and which are quite different from the effects of mitral stenosis, could be produced by traction at the mitral ring (cf. Fig. 1). Traction also tends to displace the position of the manometer cannulae, especially in the left auricle, where the pressure level could be varied at will by application of suitable traction.

A diminution in the volume of the left auricle and left ventricle occurs with most methods of producing a mitral stenosis. At the same time there is a tendency to force blood into the left ventricular cavity. These changes also will lead to artefacts.

When mitral stenosis is produced by compression of the A-V ring there is a tendency to occlude the left circumflex coronary artery,

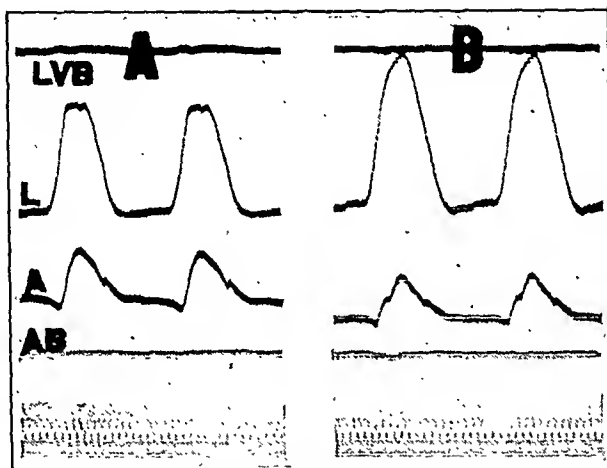


Fig. 1.—Pressure curves from aorta, A, and left ventricle, L, showing result of improper production of mitral stenosis which leads to concomitant aortic stenosis. Segment A is control; B, after mitral and aortic occlusion. LVB and AB base lines for left ventricular and aortic pressure curves respectively. Time below, each double vibrations, 1/50 sec. Note that in segment B the level and amplitude of the left ventricular pressure curve rose while they fell in the aortic curve; note also the anacrotic interruption which develops in the latter curve.

leading at once to serious undesirable disorders of the heart. Bernheim³ (1909), Schlepelmann¹⁸ (1912) and Cutler, Levine and Beek⁶ (1924) have modified the suture method to avoid this difficulty.

METHODS

In the present research a ligature method was employed to produce the mitral stenosis which with due care minimized the foregoing artefacts. The circumflex coronary artery was avoided by placing two ligatures on the auricular side of the A-V groove, but close to it. One of the ligatures was fastened to the anterior wall of the left auricle near its junction with the aorta, the other to the posterior wall of the left auricle near the interauricular groove. The two ligatures were kept in place by threading them through a series of loops fastened to the wall of the left auricle close to the A-V groove. Traction on these ligatures caused a constriction, the extent of which could be varied up to "button-hole" proportions without inter-

fering with the coronary supply of the ventricles* and without producing a concomitant aortic stenosis. The absence of aortic stenosis was shown by the parallel changes in the pressures of the aorta and left ventricle unlike the changes seen in Fig. 1, and by repeating the traction post mortem. The patency of the

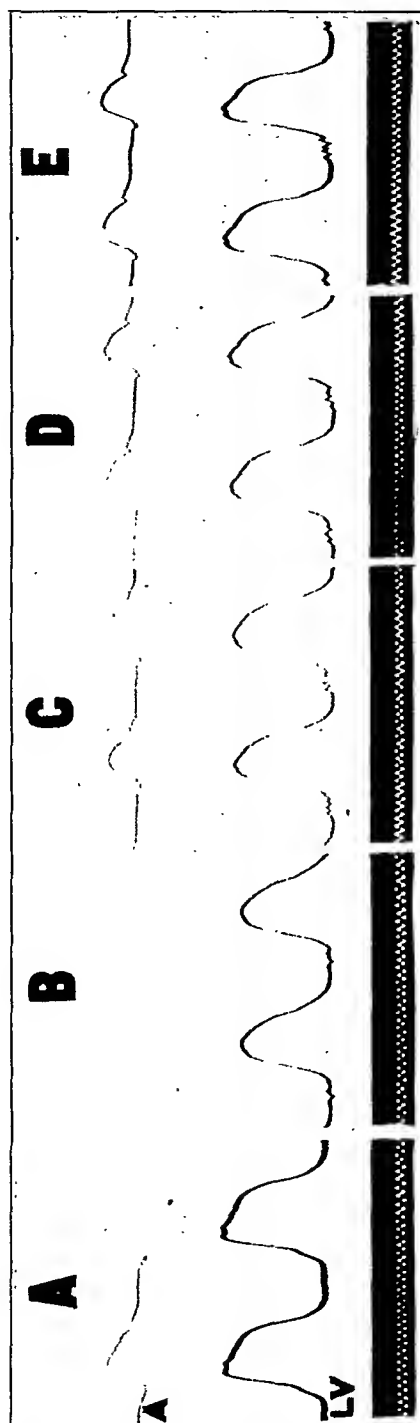


FIG. 2.—Pressure curves from aorta, A, and left ventricle, LV, showing immediate and later effects of mitral stenosis. Segment A is control, B, immediately and C, D, and E various periods within ten minutes after mitral stenosis produced. Time as in Fig. 1. Note appearance of presystolic oscillations in segments B, et seq.

coronary vessels was similarly tested post mortem. Care was taken to make the stenosis slowly and steadily with a minimal displacement of the heart. In this way traction effects were avoided or at least minimized. It was not possible to

*An unavoidable interference occurred with the blood supply to the left auricle which was not serious, we believe, because of the abundant Thebesian supply.

avoid the deformation and alteration in size of the left auricle and ventricle, but the effects of this complication are easily evaluated and do not interfere with the analysis of the effects of the mitral stenosis.

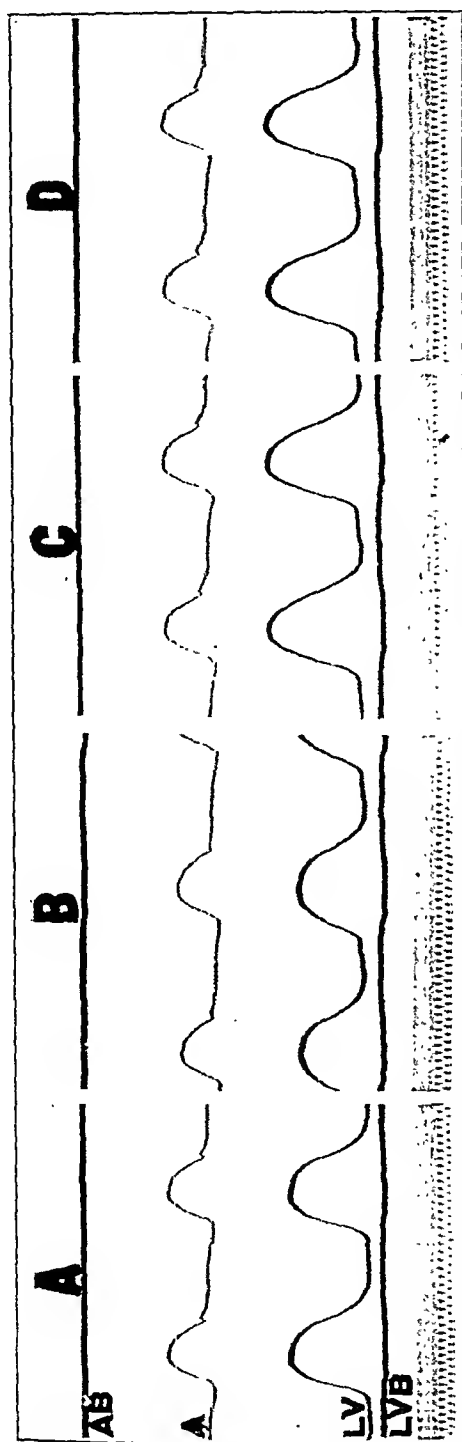


Fig. 3.—Pressure curves from aorta, *A*, and left ventricle, *LV*, showing immediate and later effects of mitral stenosis. Segment *A* is control, *B* immediately and *C* and *D* later periods after mitral stenosis. *AB* and *LV* and time as in Fig 1.

The changes in the pressure pulses following mitral stenosis were studied by registering the curves on bromide paper with manometers of the Wiggers' pattern²⁰ (1928). The experiments were made on twenty-two anesthetized dogs with chest open and artificial respiration. Simultaneous pressure records were obtained without parallax with the duo-slit lamp of Katz and Baker¹² (1924) in the following

combinations: left ventricle and aorta; left ventricle and left auricle; aorta and left auricle; left auricle and pulmonary artery; pulmonary artery and right ventricle; pulmonary artery and aorta. The manometers were inserted in the usual manner (cf. Wiggers,²¹ 1928) except for the following slight modifications: the manometer for the left auricle was inserted via a branch of the left lower pulmonary vein; the manometer for the pulmonary artery was inserted directly through the wall (cf. Katz and Weinman,¹⁵ 1927), or via the left pulmonary artery so that the opening was within 1 cm. of the semilunar valves. The sensitivity of the manometers was determined but the curves were not calibrated as we were interested only in relative changes. In several experiments direct readings of the right and left auricular pressures were made with saline manometers.

RESULTS

(a) *Effect on heart rate and the duration of the systolic phases.*—The changes in heart rate were analyzed in detail in 63 experiments made on 15 dogs. In most of these experiments no essential change in rate occurred (e.g., Figs. 4, 6 and 7). In 20 experiments the rate

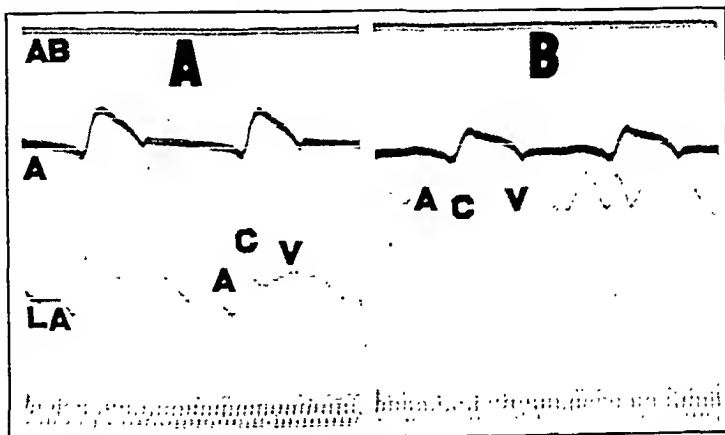


Fig. 4.—Pressure curves from aorta and left auricle showing effect of mitral stenosis. Segment A is control; segment B, immediately after mitral stenosis. AB aortic base line, A, aortic pressure curve; LA, left auricular pressure curve with so-called A, C and V waves labelled. Time as in Fig. 1.

was slowed (e.g. Figs. 3, 8), in some markedly. A slight increase in rate occurred in seven experiments (e.g. Fig. 2). Sectioning the vagi did not alter the rate response, indicating that the vagi had little to do with the rate changes. Manipulation of the auricles or traction on ligatures without producing a stenosis caused no changes in heart rate. It would seem that the rate changes, when they occurred, were caused by an alteration in the blood supply to the sinus node.

An abbreviation of total systole of the left ventricle was noted in 20 out of the 29 experiments analyzed (e.g. Figs. 2, 3)—in some instances this occurred despite a lengthening of the cycle (e.g. Fig. 3). In six experiments systole remained unchanged presumably because the tendency of the slowing in heart rate to prolong systole balanced the tendency for the stenosis to abbreviate systole. In the three experiments where the slowing of the rate was most marked systole was prolonged.

The changes in the ejection phase of the left ventricle were similar to those in total systole, i.e., an abbreviation in 29 out of 36 experiments in which it was measured (e.g. Figs. 2, 3, 4 and 8), no change in four, and a prolongation in three. The changes in the isometric contraction phase were less striking; a slight abbreviation was found in 16 out of 29 experiments measured, no change in 10, and a slight prolongation in three.

The striking abbreviation of systole and ejection of the left ventricle could be explained either (1) by the decrease in initial distention of the heart which has been shown to produce this change (Wiggers and Katz,²² 1922) or (2) by the direct action of the diminished coronary flow following mitral stenosis which accompanies the fall in aortic pressure. Our observations showed a similar decrease in systole and ejection in the right ventricle in every experiment where these phases were measured, i.e., four experiments in which systole was measured

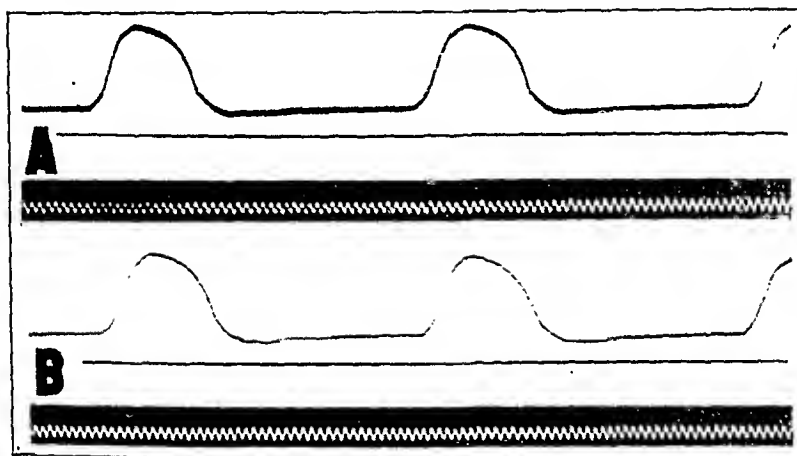


FIG. 5.—Pressure curves from left ventricle during vagus slowing showing effect of mitral stenosis. Segment A is control; B, immediately after mitral stenosis. Time as in Fig. 1. Horizontal lines were inked in to permit comparisons of the gradient of curves during diastole.

and 15 experiments in which ejection was measured (e.g. Figs. 6, 7 and 8). The fact that this abbreviation occurred in spite of an increased distention of the right ventricle in several instances (e.g. Fig. 6) would indicate that the abbreviation of systole and ejection in both ventricles were caused to a large extent by the diminution in coronary flow which follows the fall in arterial pressure.

(b) *Effects on left auricular, left ventricular and aortic pressure curves.*—1. Immediate effects. On a priori grounds, a high-grade obstruction at the mitral orifice should diminish the filling of the left ventricle and as a consequence the initial pressure and the maximum pressure developed by the left ventricle during contraction should decrease. The aortic pressure level and pulse pressure should be lowered for the same reason.

A decrease in the pressure developed during contraction by the left

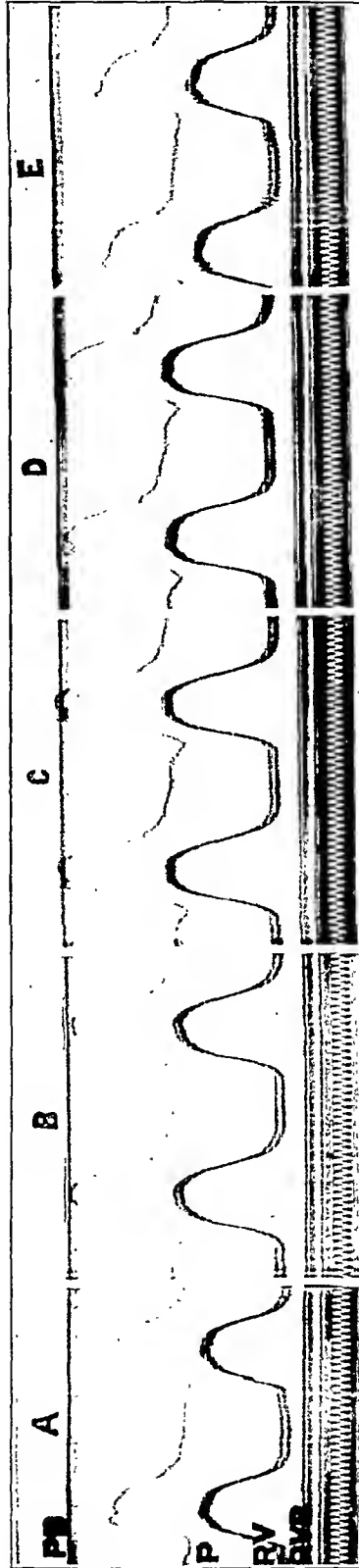


Fig. 6.—Pressure curves from pulmonary artery, P, and right ventricle, RV, showing immediate and later effects of mitral stenosis. Segment A and E are controls; B, immediately after mitral stenosis; C, D, later during mitral stenosis. PB and RVB are base lines for pulmonary arterial and right ventricular pressure curves. Time as in Fig. 1.

ventricle was found consistently just after obstructing the mitral orifice. This change was sometimes accompanied by a fall in initial pressure (cf. Fig. 2 *A* and *B*), but in most instances the initial pressure either remained unchanged or increased slightly (cf. Fig. 3 *A* and *B*). This unexpected change in initial tension is caused by an unavoidable artefact. The method of producing the stenosis leads to a deformation of the ventricular cavity which tends to increase the ventricular pressure temporarily by tending to decrease the ventricular volume, and this artefact counterbalances the tendency for the initial pressure to drop as a result of a decrease in filling. It is also possible that the change in position of the heart in relation to the manometer cannula may be the cause of the artefact.

In several experiments presystolic oscillations were recorded on the left ventricular pressure curve (cf. Fig. 2). The aortic pressure level and also the amplitude of the pulse decreased following stenosis in practically all cases (e.g. segment *B*, Figs. 2, 3, 4 and 8). This fall in

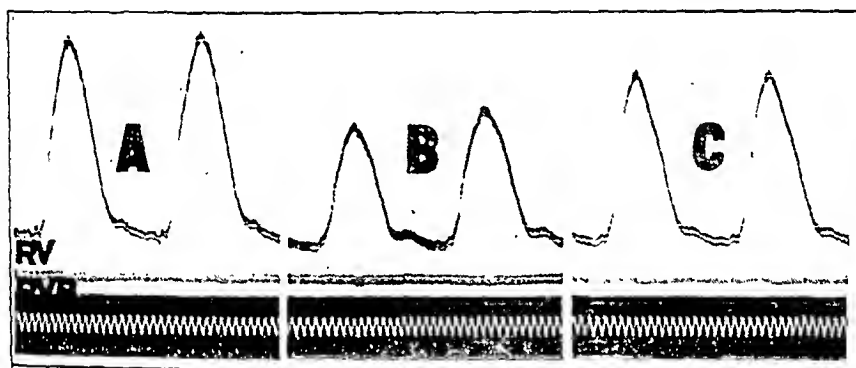


Fig. 7.—Pressure curves from right ventricle, *RV*, showing immediate and later effects of mitral stenosis. Segment *A* is control. *B* immediately after mitral stenosis. *C*, later during mitral stenosis. *RVB*, base line for pressure curve. Time as in Fig. 1.

aortic pressure level would tend to cause a decrease in the coronary flow. In several experiments, however, there was an elevation of the diastolic pressure although the systolic and pulse pressures decreased and the heart rate remained unchanged. This rise in diastolic pressure was apparently caused by a reflex vasoconstriction, since sectioning the vagi abolished it entirely.

2. Compensatory Effects.—The decrease in pressure development of the left ventricle and the lowering of the pulse pressure and pressure level of the aorta were not permanent, but after a variable time these pressures tended to increase again toward (e.g. Figs. 2, 3 and 8), and occasionally beyond, normal values (e.g. Fig. 3). Four mechanisms by which this change was brought about suggest themselves. In the first place, the elevation in the left auricular pressure which we found in every instance when traction effects were eliminated (e.g. Fig. 4) tends to overcome the handicap of the increased resistance to flow offered by the mitral stenosis. In the second place, the pumping action of the

left auricle is augmented as a result of the auricular distention. This augmentation in auricular activity goes hand in hand with the auricular distention. It is demonstrated by the increase in the *A* wave of the left auricular and left ventricular pressure curve (cf. Figs. 2 and 4). In the third place, there is a consistent prolongation of the time for filling which accompanies the abbreviation of systole. The ventricle therefore has not only a greater filling pressure head but also a longer time to fill. In the fourth place, there is an augmentation in the aspiration action of the ventricle (cf. Katz,¹¹ 1930). With filling hindered the relaxing ventricle will cause a greater drop in pressure at the start of filling, thereby increasing the pressure difference between the auricle and ventricle and so tending to facilitate the flow of blood. That this mechanism is operating is suggested by the fact that the difference in level between the start and end of filling is increased in every instance after mitral stenosis (compare segment *A* with segment *B C D* of

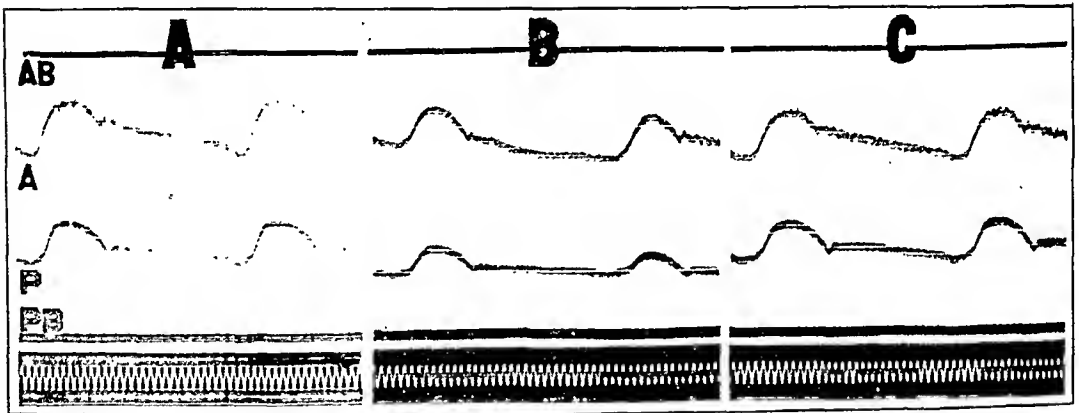


Fig. 8.—Pressure curves from aorta, *A*, and pulmonary artery, *P*, showing immediate and later effects of mitral stenosis. Segment *A* is control; *B* immediately after mitral stenosis; *C* later during mitral stenosis. *AB* and *PB* are base lines for aortic and pulmonary arterial pressure curves. Time as in Fig. 1.

Fig. 3). Part of this difference may be due to increase in auricular activity; however in certain experiments where a vagal slowing was produced and the auricular contribution minimized a similar increase in the difference in pressure level between the beginning and end of diastole was found (cf. segments *A* and *B* of Fig. 5). In Fig. 5 this increase in the pressure difference is caused by a greater drop at the start of filling and not by any rise at the end of filling as might be expected if an augmentation in auricular contribution were the cause.

(c) *Effect on right ventricular and pulmonary arterial pressure curves.*—Analysis of our experiments show two opposite effects on the right ventricular and pulmonary arterial pressure curves. In some experiments the initial pressure (and the pressure level in the right auricle) rises, and accompanying this there is an increase in the pressure development in the right ventricle (e.g. Fig. 6), and an increase in the systolic, diastolic and pulse pressures of the pulmonary artery

(e.g. Fig. 6). This is in agreement with the findings previously reported by us¹³ (1929) in stenosis of the aorta. The cause is, of course, the "damming back" of blood in the pulmonary circuit and right ventricle. On the other hand, in other experiments the initial pressure and pressure development of the right ventricle decreased after mitral stenosis (e.g. Fig. 7) and with it the pressure level and pulse pressure of the pulmonary artery also decrease (e.g. Fig. 8). This change is attributed in part to the decrease in flow in the systemic vessels and coronaries leading to a diminution of the venous return to the right heart; in part this change must also be ascribed to the depression of both ventricles caused by the lowered coronary flow. The last factor is very important as it is the chief difference which exists between these mitral stenosis experiments and those of stenosis of the aorta previously reported. In a few experiments the adjustment between the effects of "damming back" on the one hand and those of reduced venous return and diminished coronary flow on the other was so nice that no changes in pressure were recorded. In many experiments the diastolic pressure in the pulmonary artery rose even though the systolic and pulse pressures fell. This combination was due to the effect of the "damming back" of blood in the pulmonary artery raising the pressure level, combined with the effect of a decreased venous return and coronary flow depressing the activity of the right ventricle of which the pulse pressure was an index. The fact that evidence of "damming back" of blood is present in some of these experiments indicates that in the intact animal such changes can occur even when the coronary flow is decreasing. This observation is contrary to Anrep's² (1925) results with the heart-lung, and shows that the heart-lung cannot be used to estimate the dynamic changes which occur in the intact circulation.

During compensation the curves gradually tended to return toward normal (e.g. Figs. 6, 7 and 8).

SUMMARY

1. A ligature method was developed to produce stenosis of the mitral orifice with a minimum of artefacts due to traction and with no interference with the coronary supply to the ventricle. The cardiodynamic changes were studied in dogs by optical manometers recording on bromide paper. The importance of recognizing, minimizing and evaluating the effects of artefacts is emphasized.

2. Experimental stenosis of the mitral orifice produced the following immediate changes:

- a. A variable amount of slowing of the heart rate in most cases.
- b. A marked abbreviation of the ejection and total systole time in both ventricles.
- c. An elevation in the pressure of the left auricle.
- d. An increase in the magnitude of the left auricular contraction.

- e. A decrease in the maximum pressure developed by the left ventricle.
- f. A variable change in the level of the initial pressure of the left ventricle (due to an unavoidable artefact).
- g. A fall in systolic, diastolic and pulse pressure in the aorta.
- h. A variable change in the pulmonary arterial and right ventricular pressures; the pressures sometimes fell, sometimes rose or remained unchanged.
- i. The occasional appearance of presystolic oscillations on the left ventricular pressure curve.
- j. A steeper gradient of pressure rise during diastasis in the left ventricular pressure curve.

3. These changes are in part the direct result of the stenosis, causing impediment of flow to the left ventricle and "damming back" of fluid in the pulmonary circuit. In part they depend on the decrease in coronary flow resulting from the fall in arterial blood pressure.

4. Compensatory mechanisms soon tend to restore conditions toward normal. Evidence is given which suggests that these compensatory mechanisms include: (a) an increase in the pressure head of the left auricle, (b) an increase in the magnitude of auricular activity, (c) a prolongation of the time for diastolic filling, and (d) an augmentation of the aspirating action of the left ventricle as evidenced by the steeper rise of the diastolic portion of its pressure curve. All these factors tend to overcome the impediment of the obstruction, thereby augmenting left ventricular filling and lessening the damming up of blood in the pulmonary circuit.

REFERENCES

1. Allen, D. S.: *Arch. Surg.* 8: 317, 1924.
2. Anrep, G. V., and Bulatao, E.: *J. Physiol.* 60: 175, 1925.
3. Bernheim, B. M.: *Johns Hopkins Bull.* 20: 107, 1909.
4. Coryllos, P., Edwards, D. J., and Bagg, H. J.: *Proc. Soc. Exper. Biol. & Med.* 21: 151, 1923.
5. Cushing, H., and Branch, J. R. B.: *J. Med. Res.* 17: 471, 1908.
6. Cutler, E. C., Levine, S. A., and Beek, C. S.: *Arch. Surg.* 9: 689, 1924.
7. Dzwankowska, H.: *J. Physiol. Path. Gen.* 22: S72, 1924.
8. Gerhardt, H.: *Arch. f. Exper. Path. u. Pharmakol.* 45: 186, 1901.
9. Gerhardt, H.: *Arch. f. Exper. Path. u. Pharmakol.* 82: 122, 1912.
10. Hirschfelder, D.: *Johns Hopkins Bull.* 19: 319, 1908.
11. Katz, L. N.: *Am. J. Physiol.* 95: 542, 1930.
12. Katz, L. N., and Baker, W. R.: *J. Lab. & Clin. Med.* 10: 47, 1924.
13. Katz, L. N., Ralli, E. P., and Cheer, S.: *J. Clin. Investigation* 5: 205, 1928.
14. Katz, L. N., and Siegel, M. L.: *Am. J. Physiol.* 89: 417, 1929.
15. Katz, L. N., and Weinman, S. F.: *Am. J. Physiol.* 81: 360, 1927.
16. Kornfeld, S.: *Ztschr. f. Klin. Med.* 21: 171, 1892.
17. MacCallum, W. G., and McClure, R. D.: *Johns Hopkins Bull.* 17: 260, 1906.
18. Schlepelmann, E.: *Deutsche Arch. f. Chir.* 120: 562, 1912.
19. Straub, H.: *Deutsche Arch. f. Klin. Med.* 122: 156, 1917.
20. Wiggers, C. J.: *Am. J. Physiol.* 86: 435, 1928.
21. Wiggers, C. J.: *Pressure Pulses in the Cardiovascular System*, New York, 1928, p. 26 et seq., Longmans, Green & Company.
22. Wiggers, C. J., and Katz, L. N.: *Am. J. Physiol.* 58: 439, 1922.

EXPERIENCES WITH THE DERMATHERM (TYCOS) IN RELATION TO PERIPHERAL VASCULAR DISEASE

I. NORMAL STUDIES*

HOWARD C. EDDY, M.D., AND HOWARD P. TAYLOR, M.D.
CLEVELAND, OHIO

THE study of the various pathological conditions of the extremities which are due to an inadequate blood supply has long been hampered by the lack of satisfactory methods of determining both the total blood supply to the part and the relative weight to be assigned in any given case to the factors of vascular occlusion and vascular spasm.

Numerous studies of the circulation of the extremities have been attempted, but none has given complete satisfaction. Slow cumbersome methods have had the additional disadvantage of gross inaccuracy. Palpation gives information for the lower extremity only in regard to gross changes in the major vessels in four situations, i.e., the femoral artery in the groin, the popliteal artery in the popliteal space, the posterior tibial at the ankle, and the dorsalis pedis. No clue is given as to the state of these vessels at other points or the possible development of anastomotic channels.

Stewart¹ studied the circulating blood volume in the extremities by elaborate calorimetric methods and succeeded in establishing a minimum value for circulating blood volume per unit weight in normal extremities. His method required an exacting technique and was not suitable for use outside the physiological laboratory. It also possessed the additional disadvantage of not giving differential results in the various regions of the extremities.

Cohen² and Stern³ introduced the saline wheal test as a measure of the blood supply in arterial disturbances of the extremities and set up clinical standards for its use. This test measures the relative speed of imbibition of an intradermal saline wheal by the surrounding tissues and hence is only an indirect index to the local blood flow.

Starr⁴ has recently brought forward the histamine test and used it rather extensively in arteriosclerosis and cases of diabetes mellitus with and without gangrene.

The Pachon oscillometer has proved a valuable adjunct to the study of vascular diseases but takes no account of the slow ooze of blood through minor vessels. In addition, the instrument is easily

*From the Department of Surgery, the Lakeside Hospital, Cleveland, Ohio.

deranged and difficult to employ in clinical work as it requires the absolute cooperation of the patient.

D'Oelsnitz and Cornil⁵ introduced the method of paralyzing the sympathetic innervation of the capillaries of the extremities by a constriction band applied for five minutes and measured the resultant effects by means of Pachon's oscillometer.

Direct measurement of skin temperature has been attempted, and recently Ipsen⁶ published a considerable series of observations based on "skin-felt" temperatures, i.e., temperatures recorded with a mercury thermometer on areas of skin previously covered for a consid-

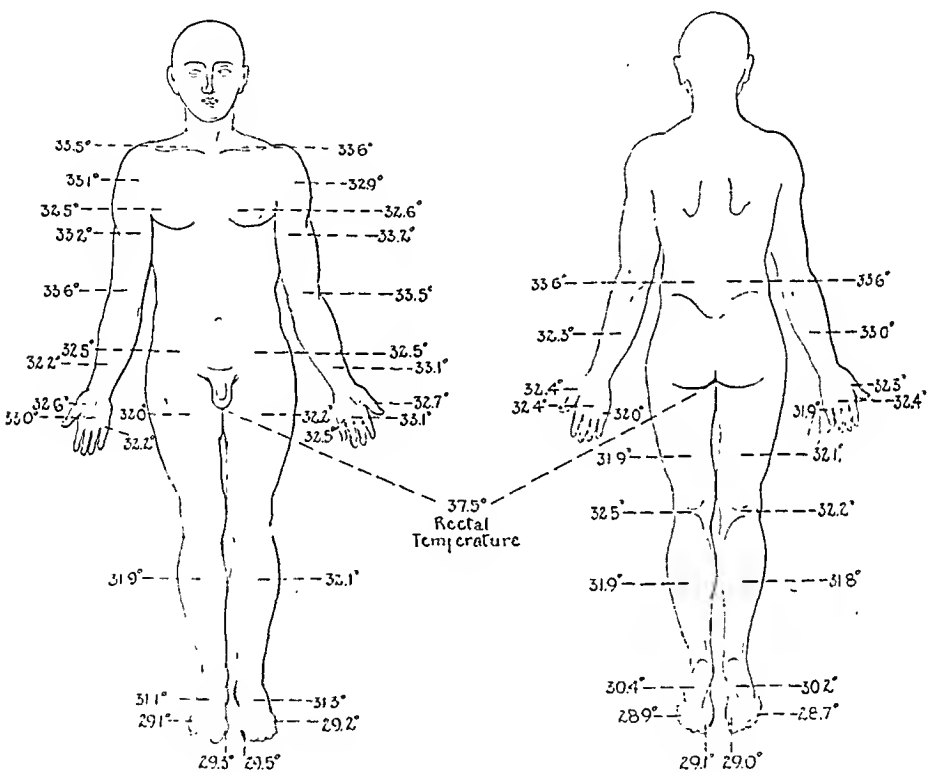


Fig. 1.—Average skin temperature of fifty normal medical students.

erable period of time by strips of felt to control the factors of heat radiation and insensible perspiration. Such a method is obviously time-consuming and does not permit virtually simultaneous observations of several areas.

Electrothermal devices have been developed and used by many investigators, notably by Benedict and his coworkers,^{7, 8} but as used in the past the junctions of the thermopile have been introduced into the barrel of a hypodermic needle. Such an arrangement, while valuable for obtaining temperature readings on the subcutaneous tissues, in its practical application is so unpleasant to the patient that it is not feasible to attempt a large number of readings on a single patient or any large series of normal readings.

The latest apparatus introduced for use in the study of peripheral vascular diseases is the Dermatherm, an improved electrothermal instrument for measuring surface temperature developed by the Taylor Instrument Company of Rochester, New York, under the direction of Dr. W. J. Merle Scott⁹ of Rochester. This instrument is described as a thermopile with its sensitivity increased by placing four couples in series. The galvanometer is calibrated directly in degrees Centigrade. The reading in degrees is added or subtracted from the reading of the constant temperature couple which is maintained within a thermos bottle. This gives the surface temperature.

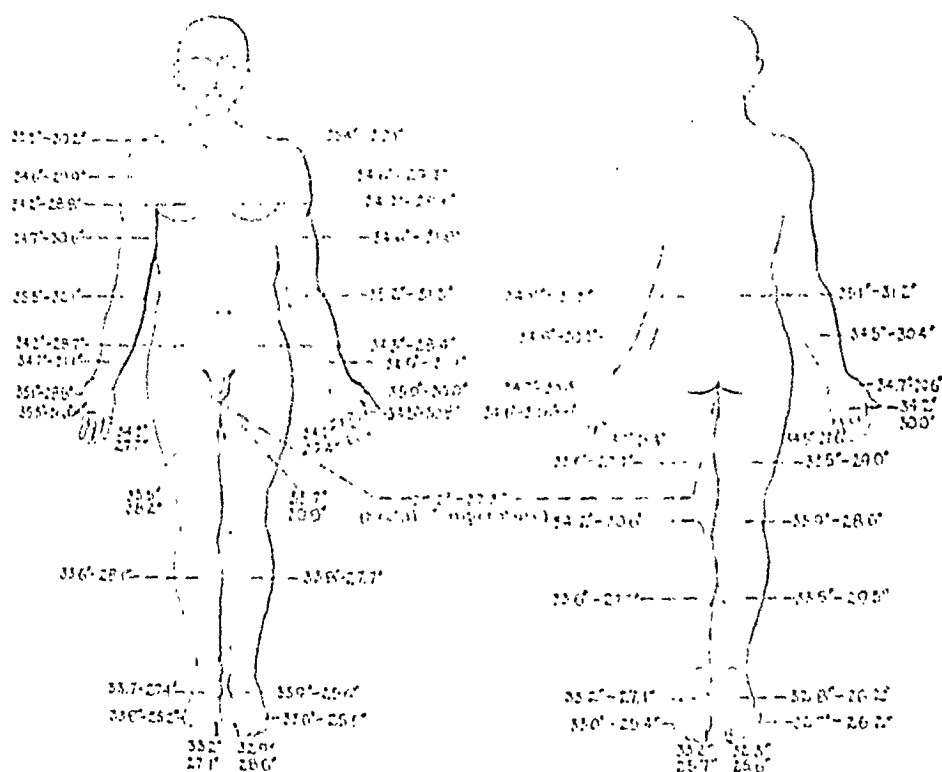


Fig. 2.—Maximum and minimum skin temperatures of fifty normal medical students.

This instrument has been used by Morton and Scott^{10, 11} in studies of the vasoconstrictor gradient of the extremities. Studies have been attempted to show the influence of spinal anesthesia and inhalation anesthetics in the reduction of the vasomotor tone of the extremities.

White¹² has introduced procaine blockage of the peripheral sympathetics as a test to evaluate the factor of vasospasm in the extremities. He describes a simple technic for obliterating completely the vasomotor gradient of the extremities.

In this paper we shall present the results of studies with the Dermatherm on fifty normal medical students.

An attempt was made to set up a normal standard for the surface temperatures of the body in healthy young adults. For this purpose fifty medical students were chosen. The rectal temperature, pulse,

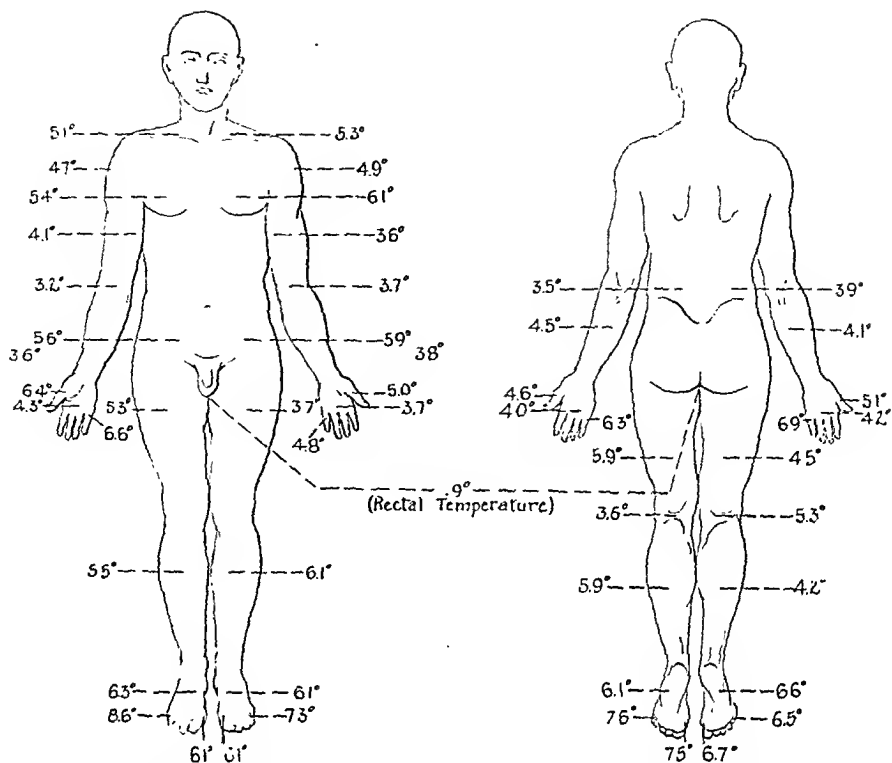


Fig. 3.—Variation of skin temperatures of fifty normal medical students.

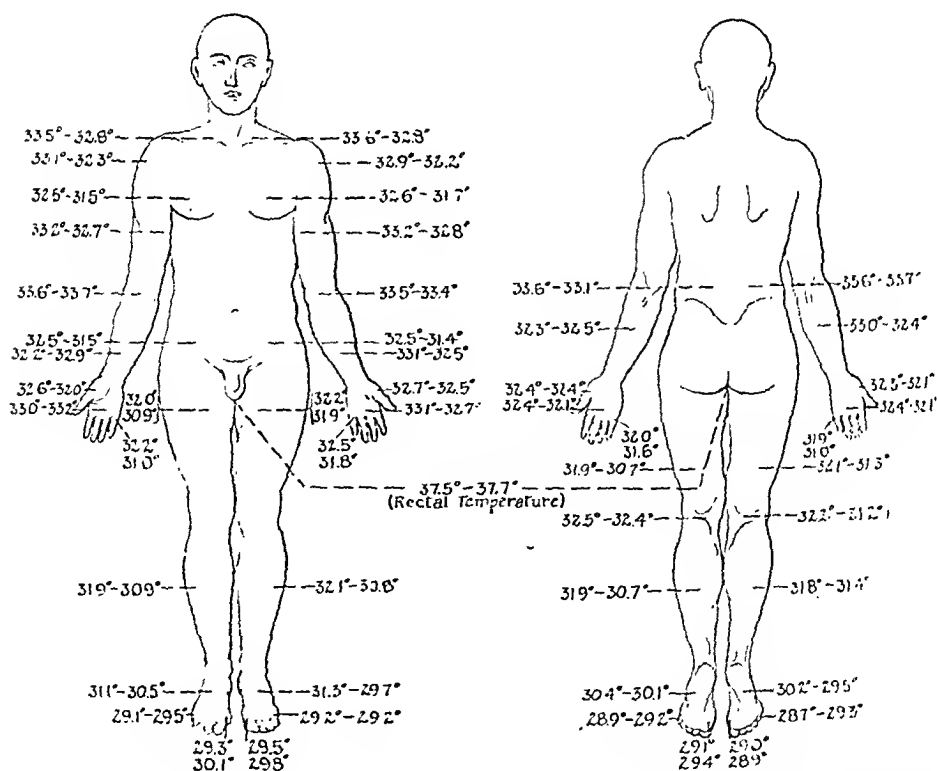


Fig. 4.—Average and mean skin temperatures of fifty normal medical students.

respiration, blood pressure, age, height, weight, and build of each student was recorded. Each student was then stripped in a room the temperature of which was 20°C ., and after five to ten minutes the surface temperature was determined for fifty-two separate points over the body and extremities.

The technic of recording was quite simple. The thermo-couple was applied gently to a skin surface for from six to eight seconds, at the end of which time the galvanometer needle was at rest. A total of approximately fifteen minutes sufficed to record the pulse, respiration, blood pressure, rectal temperature and fifty-two surface temperature readings. The extreme ease with which these readings could be taken

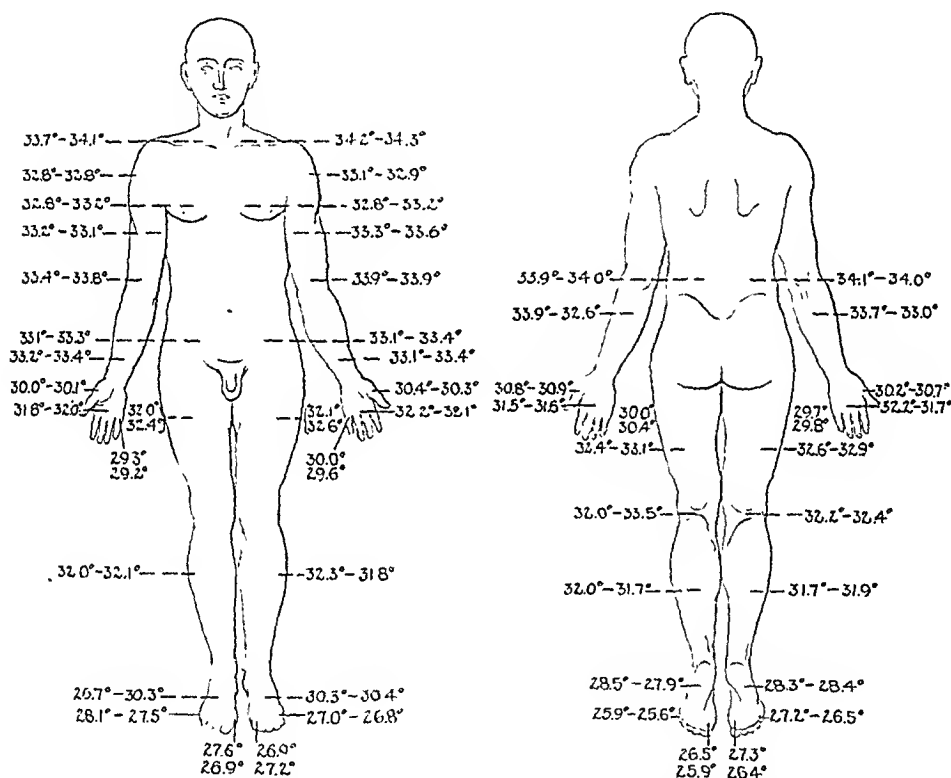


Fig. 5.—Effect of prolonged exposure of skin surface of five normal medical students to air at room temperature.

made possible the recording of a fairly complete series of skin temperatures on a large group of students. These results are presented in graphic form in Figs. 1, 2, 3, and 4.

DISCUSSION

An average of fifty determinations showed no difference between the two sides and no definite development of a vasomotor gradient in the upper extremities. In the lower extremities below the knee there was a definite development of a vasomotor gradient, the foot being one to two degrees below temperatures at the popliteal space. Temperatures at the base of the great and small toe were from two to three degrees below those in the popliteal space.

A considerable number of rather slender individuals were encountered with a moderate hypotension and a tendency to cyanosis in the extremities who showed a marked development of vasomotor gradient in the lower extremities and to a lesser extent in the upper extremities. It must be emphasized that in none of these individuals was there evidence of a pathological condition. They were merely individuals of the asthenic habitus. The extreme range in temperature variation was four to five degrees for the body, four to six degrees for the hands, and six to eight degrees for the feet. A comparison of the average and mean values tended to show that the most pronounced divergences from the normal were in the increased values found for the hands and the markedly decreased values found for the feet.

Stated simply, the "sports" were individuals with hot, moist, flushed hands and the individuals with cold, clammy, cyanotic feet.

Further study with the Dermatherm was undertaken to determine the effect when a longer period was allowed for the skin temperature to come to equilibrium with that of the air of the room. For this purpose a group of five medical students was tested as in the previous series. They then remained nude for one hour at room temperature (20° C.) and were again subjected to a complete series of skin temperature measurements. No really significant variations were observed after an exposure of one hour at a temperature of 20° C. These results are summarized in Fig. 5.

CONCLUSIONS

An attempt to establish normal skin temperature averages for a large number of definite points over the body and extremities by studies on fifty normal medical students with the Dermatherm (Tyce) resulted in the determination of an average value of 32.5° C. for the body after short exposure to the air with reduction of one to two degrees for the upper extremities and two to three degrees for the lower extremities. The vasomotor gradient is most pronounced in the hands and below the knees. The range of temperature variation of four to five degrees over the body, four to six degrees over the hands, and six to eight degrees over the feet suggests that no accurate average standard can be set up according to which all patients should be arbitrarily judged. The Dermatherm is, however, a compact instrument, simple and quick in its operation and apparently very accurate. Comparative studies on the same patient with the Dermatherm to determine the vasomotor gradient, occlusion index, etc., by use of various means of temporarily or permanently paralyzing the sympathetic supply to the peripheral vessels should prove of great value in estimating the relative part played by vaso-occlusion and vasospasm in the individual case of peripheral vascular disease.

REFERENCES

1. Stewart, G. N.: Studies on the Circulation in Man. VII. The Blood Flow in the Feet, *J. Exper. Med.* 18: 354, 1913.
2. Cohen, Milton B.: Intracutaneous Salt Solution Test. Preliminary Report of a Simple Method for Determining the Efficiency of the Circulation in the Extremities, *J. A. M. A.* 84: 1561, 1925.
3. Stern, Walter G.: The Saline Wheal Test as a Measure of the Blood Supply in Arterial Disturbances of the Extremities, *Ohio State M. J.* 24: 126, 1928.
4. Starr, Isaac: Change in the Reaction of the Skin to Histamine as Evidence of Deficient Circulation in the Lower Extremities, *J. A. M. A.* 90: 2092, 1928.
5. D'Oelsnitz, M., and Cornil, L.: Étude oscilométrique des réactions vasomotrices d'un segment de membre après compression à la Bande d'Esmach, *Compt. rend. Soc. de biol.* 82: 146, 1919.
6. Ipsen, J.: Des méthodes qui permettent d'étudier les fonctions des artères périphériques, *Acta chir. Scandinav.* 65: 226, 1929; Recherches sur les artères à l'état pathologique, *Acta chir. Scandinav.* 65: 341, 1929; Les artères et l'anesthésie, *Acta chir. Scandinav.* 65: 487, 1929.
7. Benedict, F. G., and Parmenter, H. S.: Human Skin Temperature as Affected by Muscular Activity, Exposure to Cold and Wind Movement, *Am. J. Physiol.* 87: 633, 1929.
8. Benedict, F. G., Koropathinsky, V., and Finn, M. D.: Étude sur les mesures de température de la peau, *J. de physiol. et de path. gén.* 26: 1, 1928.
9. Scott, W. J. M.: An Improved Electrothermal Instrument for Measuring the Surface Temperatures, *J. A. M. A.* 94: 1987, 1930.
10. Morton, John J., and Scott, W. J. M.: The Measurement of Sympathetic Vasoconstrictor Activity in the Lower Extremities, *J. Clin. Investigation* 9: 235, 1930.
11. Scott, W. J. M., and Morton, J. J.: Obliteration of Vasomotor Gradient in the Extremities Under Nitrous Oxide, Oxygen, Ether and Tribromethyl Alcohol Anesthetics, *Proc. Soc. Exper. Biol. & Med.* 27: 945, 1930.
12. White, J. C.: Diagnostic Blocking of Sympathetic Nerves to Extremities With Procaine. A Test to Evaluate the Benefit of Sympathetic Ganglionectomy, *J. A. M. A.* 94: 1382, 1930; and *International Abstracts of Surgery* 51: 384, 1930.

THE DURATION OF ELECTRICAL SYSTOLE AS AN INDEX OF MYOCARDIAL EFFICIENCY*

WILLIAM DOCK, M.D.
SAN FRANCISCO, CALIF.

BAZETT¹ noted that the studies of Patterson and Starling indicated a close relationship between the duration of systole and the degree of dilatation of the heart. Numerous physiologists have studied the relation of systole length, measured from mechanical or electrical records, to the heart rate, and several formulas have been evolved to express this relationship. This phase of the problem has been reviewed by Wiggers² and more recently by Cheer and Li,³ who reported on the duration of electrical systole in 178 Chinese subjects. In a preliminary paper on patients with cardiac failure, Cheer⁴ brings forward evidence which strongly supports Bazett's view that the duration of systole may be a reliable criterion of cardiac dilatation. In brief, the systolic index was definitely greater in the patients with cardiac failure than in the normal controls. The most extensive work on this problem is that of Fridericia,⁵ who also observed a prolongation of systole in certain cases of cardiac failure.

In order to be of value to the clinician any index of cardiac efficiency must vary with the severity of physiological impairment and of symptomatic distress. It is also very desirable that there shall be but little overlapping of the range of indices of normal and of pathological conditions. Thus, the vital capacity is of value since very few normals have readings of less than 80 per cent and practically no bedridden cardiac patients have 60 per cent of the predicted vital capacity. In order to reexamine the value of the systolic index I have measured a relatively small series of tracings of three groups of cases: (1) clinic patients of various ages, with vital capacities over 80 per cent, normal electrocardiograms, and no demonstrable cardiac disease; (2) a similar group in which there was a left axis deviation in the electrocardiogram, but also without symptoms of cardiac failure (these patients were all ambulatory); (3) a group of patients with normal electrocardiograms or with left axis deviation, but with vital capacity less than 51 per cent of normal (these patients were all under treatment for cardiac failure). The series was small because it was immediately evident that while the average index was prolonged in cardiac disease, the normal and pathological indices overlapped in a considerable percentage of each group and that there was

*From the Department of Medicine, Stanford University Medical School, San Francisco.

practically no difference between the group with left axis deviation without other evidence of heart disease and the group with advanced myocardial failure.

METHODS

The cases were taken in alphabetical order from the electrocardiographic files. The Q-T and R-R intervals were measured in the three standard leads, unless the T-wave was absent in one lead, as occasionally occurred. Two formulas were used to calculate the length of systole in terms of heart rate: $K = S / \sqrt{C}$, and $K = S / \sqrt[3]{C}$, where K is the systolic index, S the Q-T interval, and C, the R-R interval. A study of the indices in the 9 fastest, and 9 slowest normal men's hearts indicated that the \sqrt{C} correction gave too high indices for the more rapid hearts. This probably explains, in part, the greater length of systole after exercise (noted by Bazett) and in women (Bazett; Cheer). However, the indices obtained in heart-block (5 cases) and in some normal patients with slow pulses suggested that below 60 per minute the $\sqrt[3]{C}$ correction gave too high an index. At 60 beats per minute the cycle length is 1 and the index is the same with either correction. It would, perhaps, be safer to use $\sqrt[3]{C}$ for cycles less than 1 and \sqrt{C} for cycles longer than 1 second. I have used this method since it gives the narrowest range of variation in each of the groups measured by me.

RESULTS

(a) *Normal Men.* In 20 patients, ages twenty-three to sixty-six years, average age 41.3 years, the average systolic index when Q-T was divided by square root of R-R interval was 0.3841, if divided by cube root of R-R, 0.3722. For the nine fastest heart rates the square root formula gave an average index of 0.400, the nine slowest an average of 0.374. With the eube root formula the averages for the same groups were 0.376 and 0.374 respectively. The formula for systolic-index adopted for use ($K = S / \sqrt{C}$ when $C > 1$, and $= S / \sqrt[3]{C}$ when $C < 1$) gave an average index (K) of 0.3714, maximum 0.401, minimum 0.347.

(b) *Normal Women.* The average age of 20 women was 34.6 years, the oldest was sixty, the youngest eighteen years. The square root formula gave an average of 0.3980, the eube root 0.3794; the final formula 0.3789, maximum 0.417, minimum 0.341. The average cycle length of the women was 0.751 sec., of the men 0.852 sec. The difference in systolic indices of male and female (0.0074) is only 2 per cent, and for this small series is not significant, particularly when the difference in cycle-length is considered. However, when 8 pairs of males and females having equal cycle length are compared, 6 women have larger indices, and only two men have indices greater than the corresponding female. On the average, the index of systolic duration of men is shorter, in this series of 8, by 0.011. I also paired 8 of Bazett's males and females, and here the same number, 6 females, had larger indices and the female average index was 0.030 larger than that of men with the same heart rates. It would seem, then, that independent of the average differences in heart rate, women have a duration of electrical systole 3 to 5 per cent greater than men.

TABLE I

| | AVERAGE AGE | AVERAGE CYCLE LENGTH | AVERAGE VALUE OF S/\sqrt{C} | AVERAGE SYSTOLIC INDEX | LARGEST SYSTOLIC INDEX | PERCENTAGE OF GROUP LARGER THAN LARGEST NORMAL | PERCENTAGE OF GROUP LARGER THAN LARGEST OF LEFT AXIS DEVIATION GROUP |
|--------------------------------|----------------|----------------------------|-------------------------------------|------------------------------|------------------------------|--|---|
| Normal Men | 41.3 | 0.852 | 0.384 | 0.371 | 0.401 | 0 | 0 |
| Men with Left Axis Deviation | 53.6 | 1.050 | 0.408 | 0.404 | 0.441 | 60 per cent | 0 |
| Men with Cardiac Failure | 62.5 | 0.751 | 0.403 | 0.402 | 0.466 | 40 per cent | 10 per cent |
| Normal Women | 34.6 | 0.751 | 0.398 | 0.379 | 0.417 | 0 | 0 |
| Women with Left Axis Deviation | 43.2 | 0.852 | 0.411 | 0.400 | 0.466 | 10 per cent | 0 |
| Women with Cardiac Failure | 48.8 | 0.704 | 0.434 | 0.409 | 0.468 | 30 per cent | 10 per cent |

Systolic Index = S/\sqrt{C} when $C \geq 1$ and S/\sqrt{C} when $C < 1$ second. The patients in the L.A.D. series were free from cardiac symptoms and had vital capacities over 80 per cent of the normal; those with failure had vital capacities 50 per cent or less.

(c) *The Duration of Systole in Abnormal Hearts.* The findings in 10 men and 10 women with left axis deviation but without heart failure and with vital capacity greater than 80 per cent, and in 10 men and 10 women with heart failure and vital capacity of less than 51 per cent (average 42 per cent) are summarized in Table 1. None of these patients had any arrhythmia except occasional ectopic beats. Hypertension was present in about one-half of the first group. From the table it is evident that the systolic index is of little value in distinguishing the failing heart from the hypertrophied one, and that 65 per cent of failing hearts have indices within the normal range. Obviously the vital capacity is a more reliable and a much more sensitive index of cardiac function. The vital capacity of the group with heart failure was less than half that of the group with only left axis deviation; the systolic index was, on the average, the same, and only 10 per cent of the decompensated patients had indices greater than the largest index of the patients of the same sex who had cardiac hypertrophy without failure. It is, however, true that an index greater than 0.450 in men or 0.465 in women is rarely seen except in badly damaged hearts.

DISCUSSION

The results of my measurements of normal hearts show that, making due correction for the differences in cycle length, there still remains a real difference in the duration of systole in men and women, systole being longer in the latter. They also show that, both in men and in women, the shift in axis deviation to the left, occurring in middle age and particularly with a rising blood pressure, is associated with a prolongation of systole although not necessarily with any fall in vital capacity or symptoms of heart failure. Also, when heart failure does occur, the duration of systole is not increased beyond the normal range in about one-third of the cases, and the average duration is not much greater than in patients with hypertension and left axis deviation who have no cardiac distress or evidence of heart disease. The systolic index is therefore not of significance in distinguishing early cases of myocardial weakness, and a normal index does not rule out severe cardiac failure.

While the findings in this short series indicate that the duration of electrical systole cannot be correlated with the signs or symptoms of heart failure, they leave certain points open for further study. A very large number of normals, of various age groups and pulse rates, must be studied in order to define the limits of the normal, and to determine whether K should be based on the square root or the cube root of cycle length at various rates, or whether the cube root is also correct for rates slower than 60 per minute.

It has been held that the duration of mechanical systole is more sig-

nificant than the duration of electrical systole. From a small series of clinical records, in which sounds and electrocardiograms were recorded simultaneously, there was strong evidence against the superiority of mechanical systole, for in patients with gallop rhythm the electrical systole was from 8 to 25 per cent longer than the Q-A₂ interval. The systolic index, based on the Q-T interval, averaged 0.395, while that based on the Q-A₂ interval averaged 0.336 sec. In four normal subjects and four compensated cases of mitral stenosis, the Q-T and Q-A₂ intervals had the same average duration. This suggested that in myocardial failure, particularly in the hypertensive patients, mechanical systole may be shortened although electrical systole is prolonged. There is some experimental confirmation of this in the work of Wiggers and Katz,⁶ who observed a shortening of mechanical systole on raising the diastolic pressure of dogs. However, they believed this to be evidence of good myocardial function.

It may be noted that my findings as to prolongation of systole in patients with left axis deviation confirm the observation of Meakins⁷; also there is fairly close agreement between the average normal figures, and the average figures in heart failure in this series and in Cheer's series of normals and his series of cases of hypertensive heart failure. Such agreement greatly increases the statistical significance of the findings in this short series.

CONCLUSION

The most satisfactory constant for the prediction of normal duration of systole at varying heart rates is obtained by the formula: $K = S / \sqrt{C}$ if C is greater than 1.0 second, and $S / \sqrt[3]{C}$ if C is less than 1.0 second. The cube root gives a more satisfactory constant, at rates between 60 and 120 per minute, than the square root of the cycle length.

There is a slight but definite difference in the duration of systole in normal men and women, even when individuals with the same heart rates are compared. Systole is 3 to 5 per cent longer in women.

In patients with heart failure the average index of duration of systole was 7 per cent greater than in normal individuals, and was the same as that of the group of patients with only left axis deviation. The average vital capacity of the first group was 94 per cent, of the left axis deviation group 86 per cent, of the heart failure group 42 per cent.

The systolic duration is not a satisfactory index of cardiac function, as only one-third of the failing hearts have systoles longer than the maximum found in a group of 20 normals of the same sex, and the duration is practically the same in hypertensive patients with left ventricular preponderance, but no evidence of failure, and in patients who are badly decompensated.

REFERENCES

1. Bazett, H. C.: An Analysis of the Time Relationships of the Electrocardiogram, *Heart* 7: 353, 1920.
2. Wiggers, C. J.: *Circulation in Health and Disease*, Philadelphia, 1923, p. 102, Lea and Febiger.
3. Cheer, S. N., and Li, R. C.: *Chinese J. Physiol.* 4: 491, 1930.
4. Cheer, S. N.: Duration of Electrical Systole (Q-T Interval) in Cardiac Failure, *Proc. Soc. Exper. Biol. & Med.* 27: 877, 1930.
5. Fridericia, L. S.: Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken, *Acta med. Scandinav.* 53: 469 and 489, 1920; and 50: 17, 1920.
6. Quoted by Wiggers (ref. 2), p. 115.
7. Meakins, J.: The Prolongation of the "S-T" Interval of the Ventricular Complex Record by the Electrocardiograph, *Arch. Int. Med.* 24: 489, 1919.

ELECTROCARDIOGRAPHIC CHANGES IN PNEUMONIA*

A. M. MASTER, M.D., A. ROMANOFF, M.D., AND H. JAFFE, M.D.

NEW YORK, N. Y.

DAILY electrocardiographic records were taken on forty-five patients with lobar, and seven patients with bronchopneumonia. Our object was to learn whether any graphic evidence of cardiac involvement occurred during the disease. This is of importance for many reasons. Most clinicians feel that the circulatory apparatus plays an important rôle in pneumonia; in fact, failure of this system is believed to be a common cause of death. Pneumonia is cited as a cause of acute and chronic pericarditis, acute myocarditis and acute endocarditis. It may be an important factor in such cardiac disturbances as tachycardia, bradycardia, premature beats, auricular fibrillation, auricular flutter and heart-block.

No direct electrocardiographic study has hitherto been made in this disease. Robinson¹ in 1912 observed a prolongation of the P-R interval in the "dying heart" of two patients with pneumonia. Cohn and Jamieson² in 1917 in their investigation of the action of digitalis in pneumonia used fifty-six patients as controls, i.e., these patients received no digitalis. In two of these, P-R and T-wave changes were found; and in eight patients T-wave abnormalities were discovered. There is, however, no exact description of what these T-wave changes consisted. We, ourselves, have only considered T-wave inversions and flat T-waves. Again, Cohn and Jamieson usually took only one or two records in each patient throughout the entire illness, but it will be shown that the changes in pneumonia are often transient, and hence daily tracings are essential in investigations of this kind. In a more recent work of Burnett and Piltz³ on the acute infections, T-wave, P-R and QRS changes were noted in six cases of pneumonia. Unfortunately these authors do not state whether their patients received digitalis. The effects of this drug must be excluded in order to be certain that the electrocardiographic changes are due to the disease itself. Two of us⁴ have recently made a preliminary report on twenty-six pneumonia patients, but this larger series is reported in more detail. Electrocardiographic records were taken every day on patients who received no digitalis either before admission to the hospital or during their stay. It should be stated at the outset that the electrocardiographic changes reported in this paper, although at times of minor degree, were always definite. The changes were gradual, either in development or in disappearance, or in both, and hence it is felt that even the minor changes

*From the Cardiographic Laboratory, and the Medical Service of Dr. Leo Kessel, the Mount Sinai Hospital, New York City.

were of significance. They are not due merely to breathing, change of position, drugs, etc. Our tracings were always taken with the patient in the supine position.

The following three cases illustrate the chief electrocardiographic findings in our series.

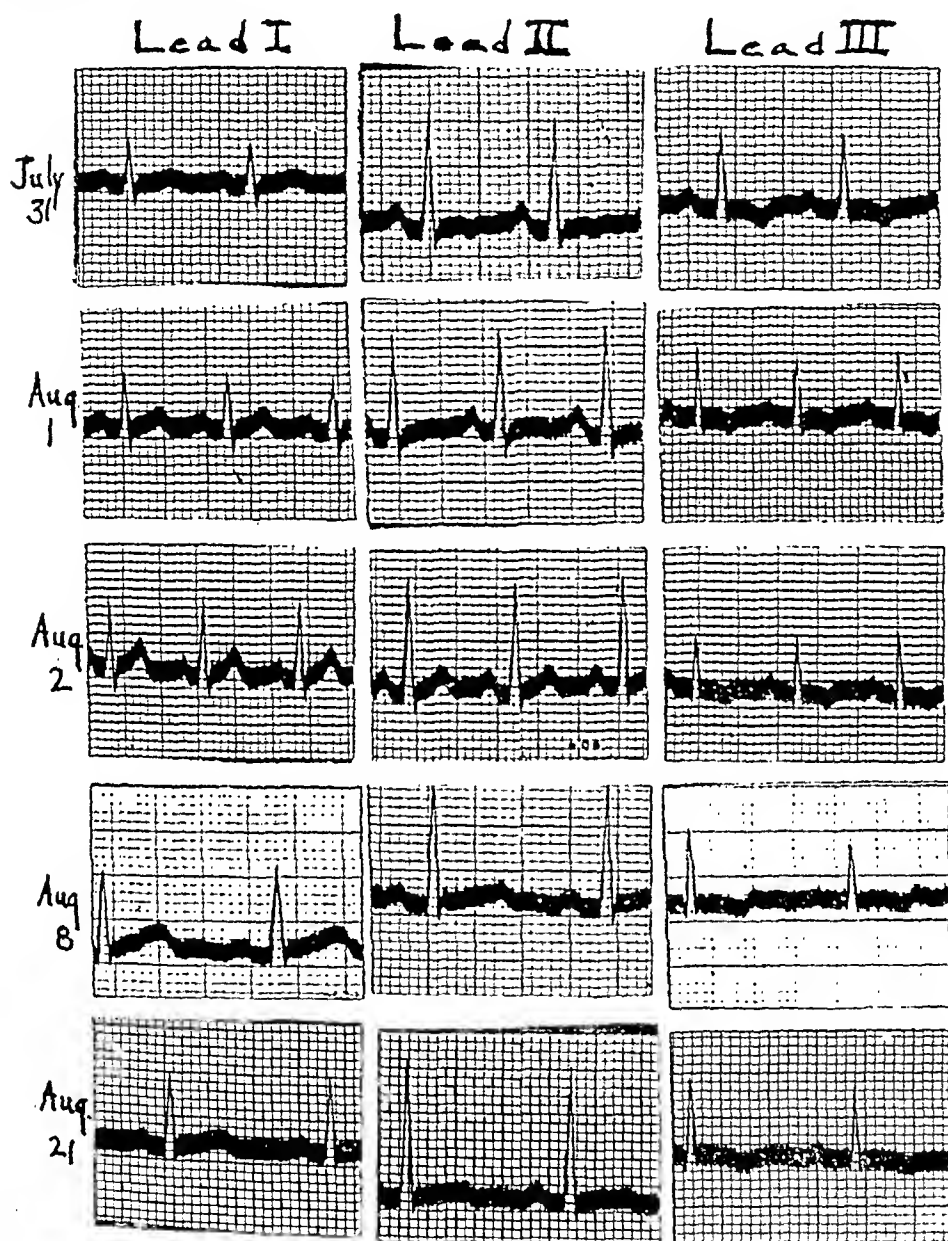


Fig. 1.—July 31, third day of illness. Temperature 103°-104.5° F., T₂₋₃ inverted.
 Aug. 1, temperature 103°-107° F., T₂ flat, T₃ inverted.
 Aug. 2, temperature 100°-105° F., T₂ normal, R-T₁₋₂ slightly abnormal.
 Aug. 8, temperature normal, R-T₁₋₂ above isoelectric level.
 Aug. 21, return visit. R-T₁₋₂ still above isoelectric level.

CASE 1.—Patient B. Mc. (316980), a girl of nineteen years, was admitted July 31, 1930, and discharged August 21, 1930. Four days prior to the hospital admission she had gone swimming and caught a "cold." Two days later a slight productive cough set in, followed by a chill. A sticking pain in the left chest then developed. On examination the patient was an acutely ill, well-developed and

well-nourished girl. Her temperature was 104° F., the pulse rate was 132 per minute, the respiration 28. In brief, signs of consolidation were found in the right upper lobe with involvement also of the right base. These findings were confirmed by the roentgen film. Examination of the heart revealed a marked tachycardia, but the heart sounds were good. A short systolic murmur was heard at the apex. No pericardial rub could be heard on admission or at any other time. On August 4, the heart sounds were slightly muffled. The temperature fell to normal on the fifth and sixth days by rapid lysis. Five of her many daily electrocardiograms are shown in Fig. 1. The inverted T-wave in Lead II, present on admission, disappeared within forty-eight hours. On the eighth of August, abnormalities of the R-T interval in Leads I and II were noted, occurring, interestingly enough, with the subsidence of fever. These R-T changes persisted throughout the stay in the hospital, and in fact were present a month later when the patient was examined at a follow-up clinic. At this visit she presented an overacting heart, and complained of some shortness of breath on exertion, easy fatigability and palpitation of the heart. None of these symptoms had been present before her illness.

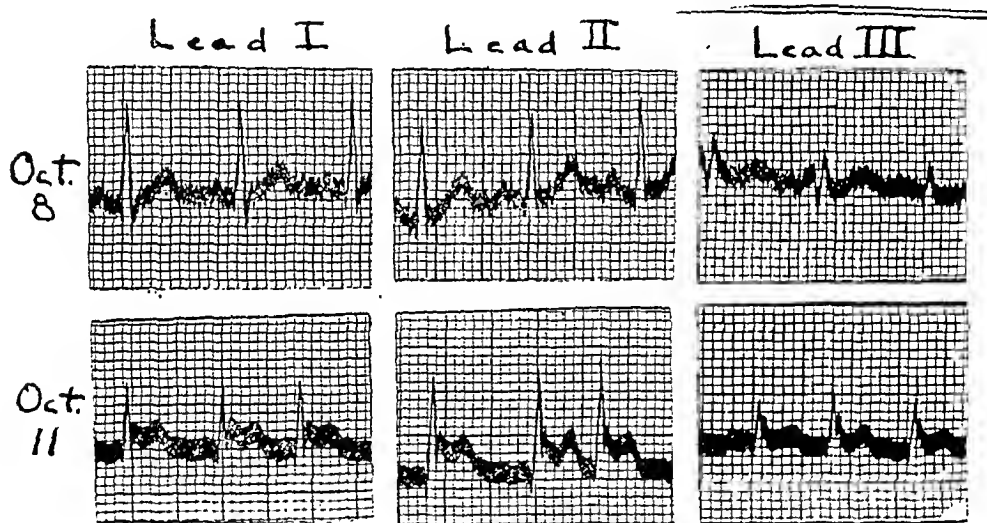


Fig. 2.—Oct. 8, sixth day of illness. Temperature 104° F., normal sinus rhythm.
Oct. 11, date of death, temperature 101° F., auricular fibrillation, R-T interval markedly abnormal.

CASE 2.—Patient P. Z. (319101), a carpenter, fifty-eight years of age, entered the Mount Sinai Hospital October 7, 1930, and died October 11, 1930. His symptoms began four days before admission with a chill, and pain in the right side of the chest, which was aggravated by cough or by deep respiration. The patient was acutely ill and was very dyspneic. The signs of lobar pneumonia were present at the right base and were confirmed by teleroentgenogram. Pneumococcus Type I was found in the blood culture. The temperature ranged between 101° and 104° F. The heart rate was rapid, the heart sounds became poor and embryocardial in character. The dyspnea, orthopnea, and cyanosis increased. An oxygen tent was utilized to relieve the cyanosis. In Fig. 2 a normal record is seen. Three days later, the day on which death occurred, a high take-off of the R-T was observed, together with auricular fibrillation and a ventricular rate of 130 to 210 per minute. The oxygen therapy produced no change in this electrocardiogram. A post-mortem examination was obtained and there were found a lobar pneumonia of the right lung, an acute fibrinopurulent pleuritis of the right lung, an acute fibrinopurulent pericarditis, and some arteriosclerosis of the aortic cusp of the

mitral valve, aortic valve and the aorta. The coronary arteries were patent throughout. There were numerous small foci of parenchymatous degeneration of the muscle fibers.

CASE 3.—Patient D. S. (317351), an eighteen-year-old Porto Rienn was admitted August 12, and discharged August 26, 1930. There was a history of cold in the head with running nose, sore throat and cough of two weeks' duration and a more recent story of fever with pain in the left chest aggravated by cough and breathing for four days. One day before admission he coughed blood-streaked sputum. He was an acutely ill boy, with a stiff neck and signs of pneumonia in the left lower lobe. His temperature on admission was 103° F. Gradually and somewhat irregularly the temperature became normal by August 19. The electrocardiograms (Fig. 3) show at first a tachycardia of 105-115 per minute, an auriculo-ventricular conduction time of 0.16 seconds and normal R-T intervals. The P-R interval slowly increased to 0.20 seconds on August 18, with a heart rate of 54 per minute;

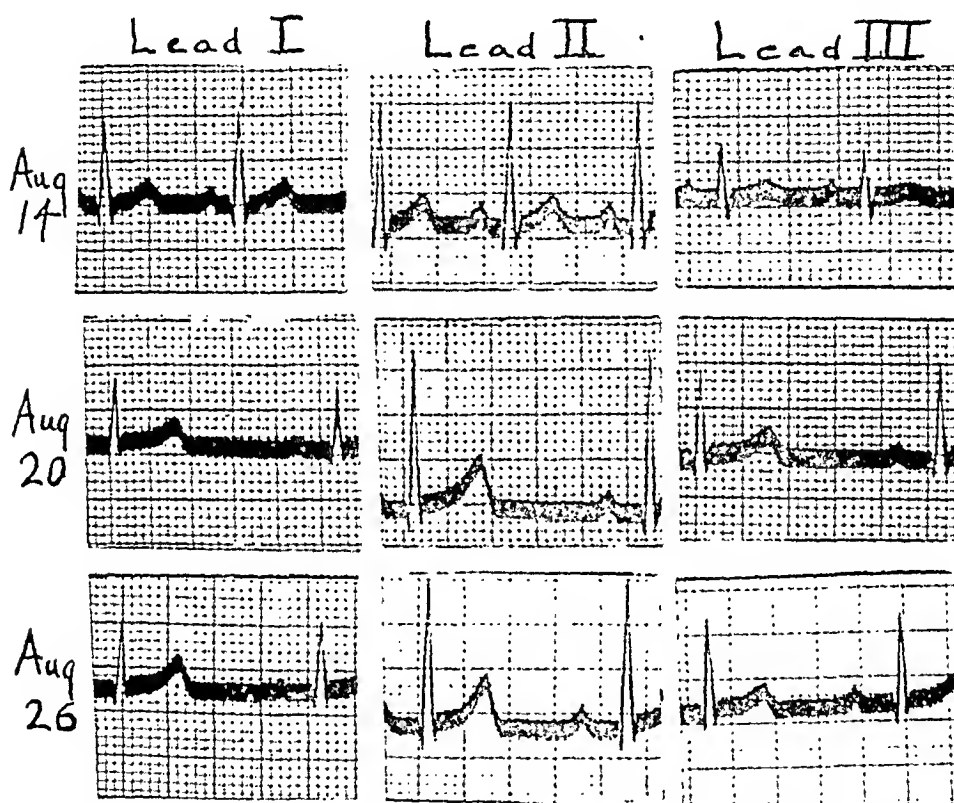


Fig. 3.—Aug. 14, sixth day of illness, temperature 98° - 103° F., P-R 0.16 seconds.
Aug. 20, temperature normal, P-R 0.20 seconds, R-T₂₋₃ abnormal.
Aug. 26, temperature normal, P-R 0.22 seconds, R-T₂₋₃ abnormal.

then 0.22 second on August 25. On August 17, R-T abnormalities had become evident. This case illustrates the onset of partial auriculo-ventricular block, R-T disturbances and bradycardia with subsidence of temperature to normal, i.e., with beginning convalescence of the patient. The P-R and R-T changes were still present on discharge.

Tables I and II summarize the electrocardiographic changes found in the series of 52 cases. The rate, rhythm, QRS group, auriculo-ventricular conduction time, T-wave, and QRS-T intervals, P-waves and ventricular preponderance were closely observed. The majority of our fifty-two patients were young adult males, only thirteen were females.

TABLE I
ELECTROCARDIOGRAPHIC CHANGES IN PNEUMONIA

| CASES | AVERAGE AGE | DEATHS | TACHYCARDIA | BRADYCARDIA | SINUS ARRHYTHMIA | LARGE-T | P-R INCREASE | INVERSION T ₁₋₂₋₃ | INVERSION T ₂₋₃ |
|---------|-------------------------------|-------------|----------------|------------------------|-------------------|-----------------|---------------------------|------------------------------|----------------------------|
| Lobar | 31 | 8 | 31 | 23 | 20 | 21 | 15 | 2 | 5 |
| Broncho | 39 | 1 | 4 | 1 | 2 | 0 | 3 | 1 | 2 |
| FLAT-T | INVERSION T ₂ ONLY | R-T CHANGES | PREMATURE BEAT | AURICULAR FIBRILLATION | AURICULAR FLUTTER | ALTERNATION QRS | CHANGED PREPONDERANCE QRS | CHANGE IN QRS | CHANGED P ₃ |
| Lobar | 3 | 9 | 42 (93%) | 1 Aur. 1 Vent. | 2 | 1 | 2 | 3 | 2 |
| Broncho | 1 | 2 | 1 (14%) | 1 Aur. | 0 | 1 | 1 | 1 | 1 |

TABLE II
ELECTROCARDIOGRAPHIC CHANGES IN PNEUMONIA

| CASES | TACHYCARDIA | AVERAGE HIGHEST RATE | BRADYCARDIA | SINUS ARRHYTHMIA | LARGE-T | P-R INCREASE | INVERSION T ₁₋₂₋₃ |
|----------------------------|--------------------|----------------------|--------------------|------------------|------------------------|-------------------|------------------------------|
| Living | 48 | 26 (61%) | 24 | 22 | 20 | 18 | 1 |
| Dead | 9 | 9 (100%) | 0 | 0 | 1 | 0 | 2 |
| INVERSION T ₂₋₃ | TOTAL T INVERSIONS | FLAT-T | INVERTED OR FLAT-T | PREMATURE BEAT | AURICULAR FIBRILLATION | AURICULAR FLUTTER | ALTERNATION QRS |
| Living | 5 | 3 | 9 (21%) | 2 | 0 | 1 | 1 |
| Dead | 2 | 1 | 5 (56%) | 1 | 2 | 0 | 1 |

An increase in the P-R interval, i.e., an increased auriculo-ventricular conduction time was a significant finding (Tables I and II) and occurred in 35 per cent of the cases. Although this delay was never so marked as one often finds in acute rheumatic fever, nevertheless it was definite. In thirteen patients the P-R interval increased to 0.20 seconds, in two patients to 0.21 seconds, in one patient to 0.22 seconds, and in two others there was a prolongation of the P-R interval to 0.24 seconds. The P-R interval increased as the patient became convalescent, in fact the highest figures were first noted on the day of discharge. No increase in the P-R interval was observed in any of the fatal cases. This is another way of stating that the delay in auriculo-ventricular conduction is a phenomenon of convalescence. Dykes⁵ in 1912, by means of jugular vein and radial artery tracings, found a temporary partial heart-block in a twenty-three-year-old patient with a lobar pneumonia.

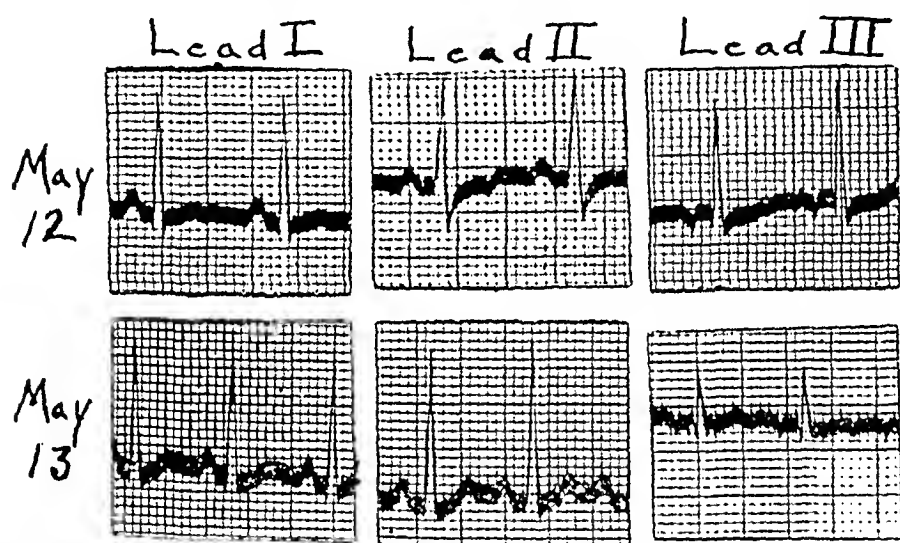


Fig. 4.—May 12, third day of illness. Temperature 100° - 101° F., T_1 flat and slightly inverted, T_{2-3} inverted, R- T_{2-3} abnormal.
May 13, T-waves practically normal, R- T_2 still abnormal.

This occurred after the crisis and lasted for four weeks. In the illustration given by Cohn and Jamieson² at the end of their paper, an increase in the P-R interval to 0.21 seconds is present in a patient in the fourth week of convalescence. A delay in conduction occurring during convalescence, was reported by Hyman⁶ in patients with influenza.

Ten patients were tested to study the effect of atropine sulphate on the auriculo-ventricular conduction time. In only two instances was there a definite decrease. In one individual a P-R of 0.20 seconds was reduced to 0.16-0.18 seconds, and in another to 0.16 seconds, on the administration of 1/50 grain of atropine sulphate intravenously.

For evidence of pericardial or myocardial impairment, close scrutiny was kept on the T-wave and RS-T intervals. Changes in each lead were followed daily. Negative T-waves in either Lead I or II were discovered in ten individuals. In three cases the inversion, or partial

inversion occurred in all three leads. Two of these patients died within two days after these changes appeared (Fig. 4). Negative T-waves in Leads I and II may be significant of an extremely toxic and fatal pneumonia. In seven patients the T-wave inversions were found in Leads II and III (Figs. 1 and 5). The mortality rate of 40 per cent in the ten patients with inverted T-waves is much higher than that of all the patients (17 per cent). Another way of emphasizing the significance of T-wave inversions is to state that of nine fatal cases the

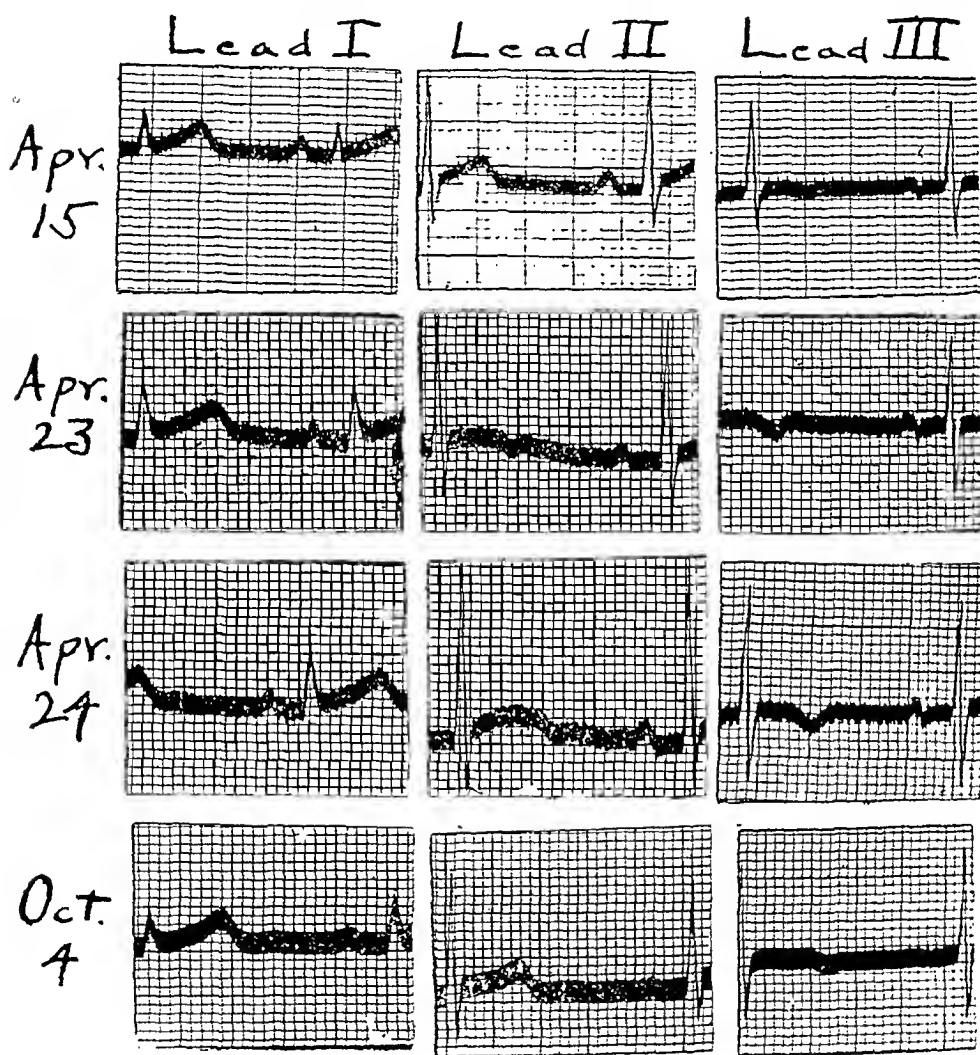


Fig. 5.—April 15, third day of illness. Temperature 100°-103° F., R-T₁₋₂ abnormal.
 April 23, temperature normal, T₂₋₃ inverted. R-T₁₋₂ abnormal.
 April 24, temperature normal. T₂ normal. R-T₁₋₂ abnormal.
 Oct. 4, return visit. R-T₁₋₂ still abnormal.

T-waves were inverted four times, or 44 per cent, whereas in those that survived the incidence was only 14 per cent (Table II).

Although the inverted T-waves were of the cove-plane shape, a contour described in coronary artery closure, no coronary artery involvement was found in any of the patients examined on the post-mortem table. Within 48 hours the inverted T-waves were normal again in all the patients who survived. In spite of their "coronary artery" con-

four the T-wave inversions in pneumonia were always slight. They thus differed from the deep T-waves so often seen in coronary artery closure, rheumatic pericarditis, and hypertension.

Flat or iso-electric T-waves were noted in four individuals. One of these patients died. Actually flat T-waves were observed twelve times, but in eight cases these subsequently became inverted T-waves and hence these patients have been enumerated among those with T-wave inversions. However, these facts give additional significance to an isoelectric or flat T-wave since it may become inverted. Flat T-waves have been considered of significance in rheumatic fever, coronary artery disease, and pneumonia.⁷

The large number of RS-T changes were of interest and may be of importance (Tables I and II). These abnormalities, when marked, have been considered almost pathognomonic of acute coronary artery

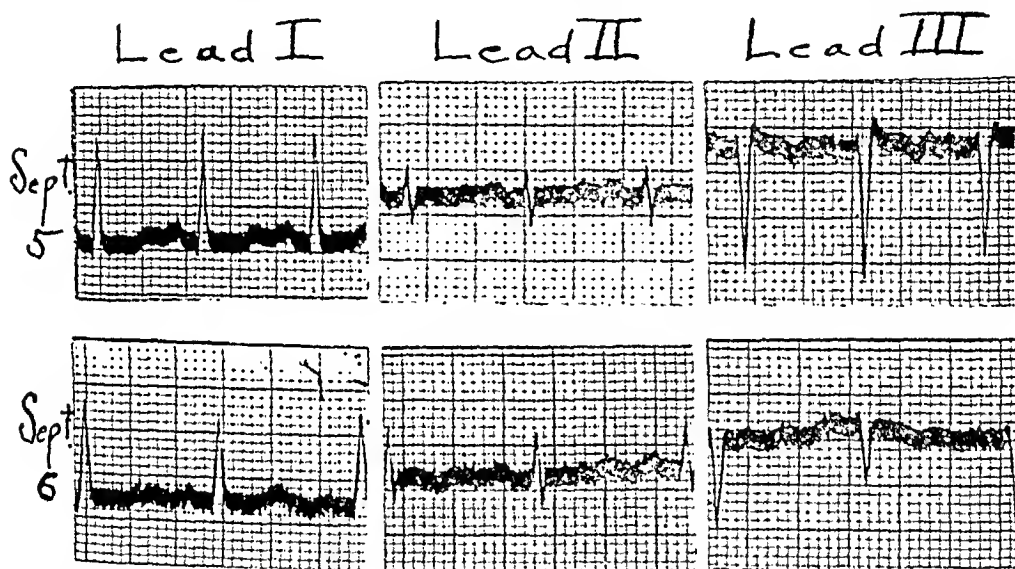


Fig. 6.—Sept. 5, fifteenth day of illness. Alternation of the QRS group.
Sept. 6, date of death.

closure,⁸ and have been described also in acute rheumatic fever.⁹ Levine¹⁰ gave one illustration of R-T abnormalities in a patient with pneumonia, which occurred after return of temperature to normal. Shearer¹¹ reported a case with similar electrocardiographic findings, also present when the patient's temperature dropped to normal. Shearer's patient recovered, and no reason was found for the R-T change.

These abnormalities in the RS-T period were observed in forty-two of the forty-five patients with lobar pneumonia (93 per cent), but only once in the seven patients with bronchopneumonia (14 per cent) (Tables I and II, and Figs. 1, 2, 3, 4, 5). It should be said that in eleven cases these changes were slight. However, that they were definite changes is proved by the fact that either at the beginning or end of the illness, the RS-T intervals were normal. In other words, they were deviations from the normal for the particular patient. One of the most

striking examples of the RS-T changes was that of Case II, previously described, who was in the hospital three days with lobar pneumonia involving the entire right lung (Fig. 2).

Although Levine¹⁰ believed that the R-T abnormality in pneumonia could be differentiated from that seen in acute coronary artery disease, it is our belief that this is impossible. However, in the former disease the R-T change returns to the base line whereas in acute coronary artery disease the T-wave becomes inverted. We have never seen this phenomenon in pneumonia.

The R-T deviations first occurred usually at about the fifth, sixth, seventh or eighth day of illness (Figs. 1 to 5). Actually they coincided with the drop of temperature and the beginning of convalescence of the patient. Usually they persisted throughout convalescence, and occasionally for weeks afterward (Figs. 1, 5). In all but four cases the R-T abnormalities were above the isoelectric level rather than below and in the great majority of cases occurred in Leads I and II only.

In thirty-five individuals a simple tachycardia was observed early in the disease, when the fever was high. The most marked tachycardia for the fatal cases averaged 159 per minute, whereas for those who recovered the average highest rate was 109 per minute. These numbers refer to the highest rates of the tachycardia noted in the patients, and not the average heart rate. The relation of tachycardia to prognosis has been noted and emphasized by clinicians for years. Osler¹² says, "Certainly the mortality increases very rapidly when the pulse rate passes 125."

A simple bradycardia was observed at some time or other in twenty-four patients. The slow rates occurred in convalescence and only when the temperature was normal. Rates as low as thirty-six beats per minute were observed. No slow rate was observed in the fatal cases. To ten patients $\frac{1}{75}$ to $\frac{1}{30}$ grain atropine was given intravenously. In seven individuals no response was obtained. One of these received $\frac{1}{30}$ grain when his rate was 120 per minute, and later during convalescence when his rate was 58 per minute. On the other hand three patients developed an increase in rate ranging from 20 to 75 additional beats per minute on administration of $\frac{1}{50}$ grain atropine sulphate.

A definite sinus arrhythmia occurred twenty-two times, usually during late convalescence, and usually when a bradycardia was present. Atropine sulphate did not alter the arrhythmia.

Change in size of the T-wave occurred in practically every patient with a bradycardia. As the heart rate became slower, the T-wave became larger. A difference of at least 2 mm. was noticed before such a change was accepted. This increase in size of T-waves was observed in twenty-one patients with lobar pneumonia and not once in bronchopneumonia.

Auricular premature beats were recorded twice and ventricular premature beats once. One of the patients showing auricular premature beats died. In one of the fatal cases an "alternation" of the QRS

complex was noted on the electrocardiographic tracing (Fig. 6) and this change was observed also in a patient who recovered. Auricular fibrillation was noted in two patients, both of whom died. Another patient who revealed an auricular flutter survived.

Changes in the P-waves and in the T-waves in Lead III were not uncommon, the former was found in three patients, the latter in eleven. A change to left axis deviation was observed three times. An alteration in the size of the QRS group was seen twice; a change from a widened QRS to one of normal dimensions, once; and a loss of notching and shurring, once.

There were nine fatal cases in this series of fifty-two patients. Post-mortem examinations were obtained in all. One case (Case 2) has already been described and it was the only one in which the heart was severely damaged, as proved by gross and microscopic examination. In seven other cases the microscopic findings showed slight, moderate, or severe degrees of parenchymatous degeneration. The changes were enough to identify the hearts as damaged but not enough to have alone produced death. These eight patients all showed R-T changes. The ninth case, one of bronchopneumonia, had an entirely negative heart. In this patient no R-T changes were present.

In general, among the nine fatal cases, the tachycardia ranged from 105 to 210, with the average of 159, in contrast to the average highest rate of 109 among those who survived. Two patients had an auricular fibrillation; one an "alternation" of the QRS group.

In a comparison (Table II) of the fatal cases with those that survived, we at once see that a tachycardia occurred without exception in the former group and that the average of the highest rates was 159. Of those patients that lived tachycardia was present in 61 per cent. The changes so commonly observed during convalescence were absent or minimal in the fatal cases, i.e., the bradycardia, sinus arrhythmia, large T-waves and increased P-R intervals. The fatal cases showed T-wave inversions in 44 per cent; the living patients in only 14 per cent. Considering inverted and iso-electric (flat) T-waves together one finds a frequency of 21 per cent among those who survived as against a figure of 56 per cent among those who died.

The bronchopneumonia group (Table I) was distinguished by the low percentage of R-T changes, i.e., only 14 per cent, whereas in the lobar pneumonia cases the percentage was 93. To us this is the most outstanding difference, but its exact significance is not clear. Tachycardia, bradycardia, sinus arrhythmia and the development of large T-waves appeared to be less common in the cases of bronchopneumonia. We say this guardedly as the number of bronchopneumonia cases is small. The patients who survived revealed tachycardia only three times and the rate was never above 115 per minute. The fatal case showed a rate of only 130 per minute.

DISCUSSION

The occurrence of increased auriculo-ventricular conduction time late in pneumonia, independent of a bradycardia, deserves consideration. Clinicians usually interpret an increased P-R interval as indicating disease of the auriculo-ventricular conduction tissues. The increased P-R interval is very often seen in rheumatic fever, and occasionally in severe toxic disease. Its occurrence late in pneumonia, when the patient is up and about, calls for an explanation. It may be that the physical activity is too much of a demand upon the weakened heart, and results in an increased conduction time. Perhaps these patients were permitted out of bed too early. The electrocardiogram therefore may prove an important guide as to the time to discharge a pneumonia patient from the hospital, or when to consider him cured. Osler¹³ pointed out that sudden death might occur when convalescence was well established. He said, "Collapse coming on a day or two after the crisis is much more grave, being usually an indication that the myocardium has sustained severe damage," and "Death may occur suddenly when convalescence is apparently well established."

The clinical implication of an abnormal R-T interval in pneumonia is not understood. In a patient with very marked changes of this sort who died an acute pericarditis and an acute myocarditis were present. On the other hand, there were at least nineteen patients with as marked R-T changes, as well as a large number with less marked R-T abnormalities, who recovered. The persistence of the R-T abnormalities throughout convalescence and even for weeks afterward may be of clinical significance. In eight patients in whom changes have persisted for weeks, there was a delayed recovery in the patient's strength, and dyspnea occurs on slight exertion. Complaints of palpitation, fatiguability, and even precordial pain, occurred long after convalescence. In two patients a second increase in the P-R interval occurred long after the auriculo-ventricular conduction time had returned to normal. In three patients a flat T-wave in Leads I or II became evident weeks after discharge from the hospital.

The significance of the electrocardiographic changes as a whole is an important one. We offer five possible explanations. The changes recorded on the graphic tracing may be a vagus nerve effect. The occurrence of a bradycardia, sinus arrhythmia, and an increased P-R interval during convalescence would lend plausibility to this theory. Atropine had some effect on the bradycardia, and auriculo-ventricular conduction time, but none on the R-T or T-wave changes. Even had the effect of this drug been more marked it still would not have proved much, for the vagus probably exerts its influence during pneumonia and during the convalescent period, just as it does in ordinary life.

It is well known that changes in position of the heart will produce changes in the electrocardiogram.¹⁴ There is no definite proof that a

change in position or rotation of the heart occurs in pneumonia, although if Coryllos¹⁵ be correct this condition occurs. His contention is that an atelectasis is present in the disease and that this draws the heart toward the affected side. In children there is good evidence that movement of the heart occurs in pneumonia.¹⁶ However, before this question is settled, frequent roentgen films of the chest must be taken on pneumonia patients.

A third explanation comes to mind when one recalls the marked frequency of the R-T changes in the patients with lobar pneumonia, and the low incidence in bronchopneumonia. It may be that electrical conduction through massively involved lung is altered, whereas in the patchy involvement of bronchopneumonia, this does not occur. The altered electrical conduction in the lung may possibly produce the R-T changes.

Experiments have been performed in which the anoxemia, rather than an organic involvement of the heart and blood vessels, is said to play the important rôle in the disease. Animals with experimentally produced pneumonia often die of respiratory failure, the heart beating rhythmically for some time after.¹⁷ Kauntz and Gruber¹⁸ produced anoxemia in animals and obtained high plateau R-T abnormalities. With a view of throwing some light on the question of anoxemia, an oxygen tent with 40 to 50 per cent oxygen saturation was used on six of our patients. Not the slightest alteration in the records was discovered. Additional evidence that the cause of the electrocardiographic changes is not an anoxemia is found in the fact that the RS-T changes persisted throughout convalescence and even after the patient's discharge from the hospital.

It is our impression that the electrocardiographic changes are caused by the toxic products of pneumonia on the heart muscle. This would apply to the T-wave changes, the R-T deviations, the impaired auriculo-ventricular conduction, bradycardia and sinus arrhythmia, but particularly to the first three of these. We feel that vagus nerve effect, displacement or rotation of the heart, altered conduction of the heart's electric current through inflamed lung, and anoxemia, are of minor importance and that an actual involvement of the heart muscle occurs. Post-mortem examination of eight of our nine fatal cases have all shown some degree of parenchymatous degeneration of the heart muscle; in one of these cases there was very marked involvement. In the ninth case there was no involvement. Moreover there may be physiological or chemical changes in the heart muscle which are not revealed by morphological study.

SUMMARY

Daily electrocardiograms were taken on forty-five patients with lobar pneumonia, and on seven patients with bronchopneumonia. The T-wave and R-T changes were very similar to those described in acute coronary

artery closure, and the P-R, R-T, and T-wave abnormalities similar to those observed in rheumatic fever. The electrocardiogram in these three diseases is therefore not specific.

In eighteen patients (35 per cent) there was a definite increase in the auriculo-ventricular conduction time, ranging from 0.20 seconds to 0.24 seconds. The impaired auriculo-ventricular conduction occurred when the temperature was normal and the patient was beginning to convalesce. Atropine sulphate affected the P-R interval only to a slight degree.

There were ten patients with inverted T-waves in Leads I or II and sixteen cases in all with either inverted or flat T-waves. These patients had a poor prognosis. The T-wave inversions occurred early in pneumonia when the prostration was marked. They showed a "cove-plane" or "coronary T-wave" contour, but were, however, always shallow and always transitory. No coronary artery involvement was found in the post-mortem examinations.

R-T abnormalities occurred in 93 per cent of the patients with lobar pneumonia. They first appeared with a fall of temperature to normal levels. The R-T deviations were similar to those observed in acute coronary artery closure but they never progressed to an inverted T-wave.

In only one case of bronchopneumonia were there R-T changes, in marked contrast to the frequency of such changes in the lobar pneumonia cases.

A tachycardia was present in thirty-five patients. The more marked the tachycardia, the worse the prognosis.

A simple bradycardia was found in twenty-four patients. The rate in these cases was often about 40 per minute, once it was as slow as 36 per minute. Atropine at times released the bradycardia.

Large T-waves were present twenty-one times, associated usually with the occurrence of a bradycardia.

A sinus arrhythmia was discovered in twenty-two individuals, and occurred in convalescence. It was sometimes present with the bradycardia, but often appeared later. Atropine had no effect on the sinus arrhythmia.

Premature beats occurred three times.

Auricular fibrillation was observed in two fatal cases.

"Alternation" of the QRS group occurred in two patients, one of whom died.

Auricular flutter was observed once. This patient survived.

Transient P-wave inversions in Lead III were recorded three times, transient T-wave inversions in Lead III alone, eleven times; a change in left axis deviation, three times; changes in the QRS group, four times.

The fatal cases showed marked tachycardia, a large number of T-wave inversions (44 per cent), and an absence of auriculo-ventricular con-

duction impairment, of bradycardia, of sinus arrhythmia, and of large T-waves.

It is suggested that T-wave, R-T, and P-R abnormalities are due to varying degrees of myocardial involvement and hence the electrocardiogram may perhaps serve as a guide as to when to permit a patient out of bed and when to consider him cured.

REFERENCES

1. Robinson, G. C.: A Study with the Electrocardiograph of the Mode of Death of the Human Heart, *J. Exper. Med.* 16: 291, 1912.
2. Cohn, A. E., and Jaudesson, R. A.: The Action of Digitalis in Pneumonia, *J. Exper. Med.* 25: 15, 1917.
3. Burnett, C. T., and Piltz, G. F.: The Electrocardiogram in Acute Infections, *J. A. M. A.* 93: 1120, 1929.
4. Master, A. M., and Romanoff, A.: Electrocardiographic Changes in Pneumonia, *Proc. Soc. Exper. Biol. & Med.* 28: 266, 1930.
5. Dykes, A. L.: Temporary Partial Heart Block, Occurring as a Sequel to Acute Pneumonia, *Lancet* 2: 1098, 1912.
6. Hyman, A. S.: Postinfluenzal Heartblock, *Med. J. & Rec.* 124: 698, 1926.
7. Master, A. M.: Low Voltage T-Waves in the Electrocardiogram, *Am. J. M. Sc.* 181: 211, 1931.
8. Rothschild, M. A., Mann, H., and Oppenheimer, R. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, *Proc. Soc. Exper. Biol. & Med.* 23: 253, 1926.
9. Pardee, H. E. B.: Clinical Aspect of the Electrocardiogram, New York, 1924, p. 84, Paul B. Hoeber.
10. Parkinson, J., and Bedford, D. L.: Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis), *Heart* 14: 3, 1928.
11. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, *J. Exper. Med.* 39: 1, 1924.
12. Rothschild, M. A., Sacks, B., and Libman, E.: The Disturbance of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *AM. HEART J.* 2: 356, 1927.
13. Porte, D., and Pardee, H. E. B.: The Occurrence of the Coronary T-Waves in Rheumatic Pericarditis, *AM. HEART J.* 4: 584, 1929.
14. Scott, R. W., Peil, A. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion, *AM. HEART J.* 5: 68, 1929.
15. Levine, S. A.: Coronary Thrombosis; Its Various Clinical Features, *Medicine* 8: 245, 1929.
16. Shearer, Margery C.: "Plateau R-T" in a Case of Lobar Pneumonia, *AM. HEART J.* 5: 801, 1930.
17. Mackenzie, J.: Diseases of the Heart, London, ed. 3, p. 287, 1921, Henry Frowde and Hodder and Stoughton.
18. Osler, Wm., and McGraw, T.: Modern Medicine, Philadelphia, 1915, p. 225, Lea and Febiger.
19. Ibid.: P. 243.
20. Einthoven, W., Fahr, G., and de Wuart, A.: Ueber die Richtung und die manifeste Grosse der Potentialschwankungen in menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch. f. Physiol.* 150: 275, 1913.
21. Master, A. M.: The Electrocardiographic Changes in Pneumothorax in Which the Heart Has Been Rotated, *AM. HEART J.* 3: 472, 1928.
22. Coryllos, P., and Birnbaum, G. L.: Lobar Pneumonia, *Arch. Surg.* 18: 190, 1929.
23. Tallerman, K. H., and Jupe, M. H.: Displacement of the Heart in Pneumonia in Childhood, *Arch. Dis. Child.* 4: 230, 1929.
24. Newburgh, L. H., Menns, J. H., and Porter, W. T.: On the State of the Respiratory Mechanism in Pneumonia, *Boston M. & S. J.* 173: 742, 1915.
25. Newburgh, L. H., and Porter, W. T.: The Heart Muscle in Pneumonia, *J. Exper. Med.* 22: 123, 1915.
26. Kountz, Wm. B., and Gruher, Chas. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. and Med.* 27: 170, 1929-30.

Department of Clinical Reports

CYST OF THE PERICARDIUM*

WALLACE M. YATER, M.D.

WASHINGTON, D. C.

SIMPLE cysts of the pericardium are practically unheard of. At least, I have been unable to find any reference in the literature to that lesion after a rather extensive search. Rarely one finds multiple cysts of the epicardium in association with chronic adhesive pericarditis or organized fibrinous pericarditis. Such a case was reported by Lauche.¹ Large cysts are found occasionally in primary sarcoma of the pericardium, as in the case of Perlstein.³ Cysticerci and echinococcus cysts

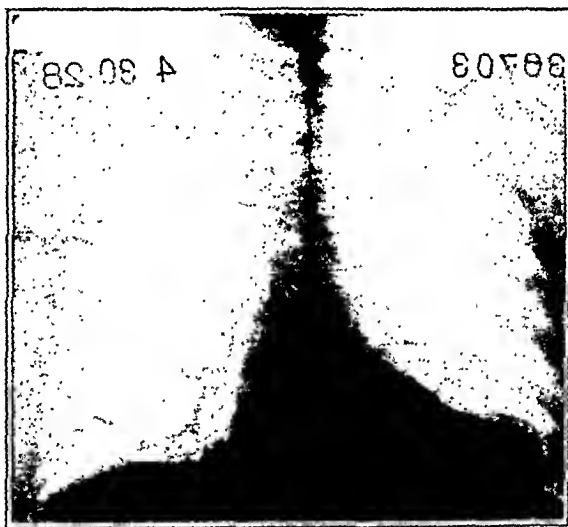


Fig. 1.—Roentgenogram of chest showing rounded lesion in region of apex of heart, which proved to be a simple multilocular cyst of the pericardium.

in the pericardial sac have been noted (Mönckeberg²). The following case is reported because of the rarity of the condition and because of the diagnostic difficulties.

CASE REPORT

The patient, a white man aged 52 years, began to have occasional attacks of mild epigastric pain in January, 1928. On April 10, 1928, while playing golf he experienced an acute attack of epigastric pain, followed by generalized abdominal soreness which finally localized in the epigastrium and right hypochondrium. The pain was constant with exacerbations, during which it radiated to the mediastinum, left shoulder and left side of neck. Physical examination on April 28 was negative

*From the Georgetown University School of Medicine and the Army Medical Museum.

except for the abdomen, which was distended and tender in the epigastrium and right hypochondrium. The heart was reported normal. Laboratory studies were negative except for the x-ray examination of the stomach and chest. There was an extensive filling defect of the stomach, most marked on the greater curvature, with retention of half of the barium meal after six hours and of one-fourth after 24 hours. Above the dome of the diaphragm and "partly overlapped by the shadow of the heart" there was a round shadow about 5 cm. in diameter (Fig. 1). The diagnosis was inoperable carcinoma of the stomach with metastasis in the left lung. The patient became progressively weaker, developed jaundice and died on May 28, 1928.

Necropsy had to be performed through an abdominal incision. There was a large ulcerating carcinoma on the greater curvature of the stomach about 3 cm. from the pylorus and several cm. in diameter, a typical adenocarcinoma microscopically. The liver weighed 3000 grams and was invaded by numerous large and small metastatic nodules. The lungs were normal. The heart was normal, but

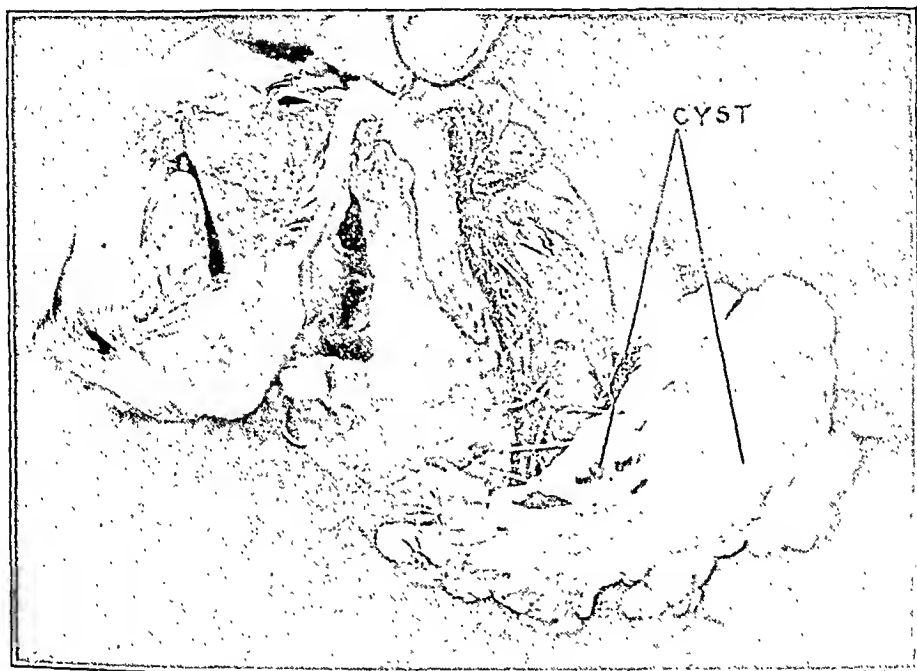


Fig. 2.—Cyst of the pericardium, reconstructed after dissection. The cyst is partially imbedded in the pericardial fat, so that its exact outline is not apparent, but the large white area indicated by the lines is the cyst.

projecting externally from the parietal pericardium at the apex and just above the diaphragm was a thin-walled, multilocular, ovoid cyst, 4.5 cm. long and 2.5 cm. thick, filled with clear, slightly yellowish, watery fluid (Fig. 2). The lining of the cyst was perfectly smooth, very thin, fibrous, and partially imbedded in the pericardial fat. It was intimately associated with the parietal pericardium and undoubtedly originated in it. There was no evidence of tumor in this region and no adhesive pericarditis. The cyst was probably derived from a lymphatic vessel of the parietal pericardium.

COMMENT

From the standpoint of roentgenographic diagnosis of the cyst one would have to decide first whether the shadow cast by it was that of a lesion in the lung or one associated with the heart. In this case it was

assumed to be in the lung because it fitted in well as a metastatic lesion from a carcinoma of the stomach. Under other circumstances a fluoroscopic study would have revealed the fact that the rounded shadow at the apex of the heart was attached to the heart. Then the diagnosis should have included the following possibilities: aneurysm of the heart, tumor of the heart or pericardium, loculated pericardial effusion, hydatid or other cyst. In this case aneurysm could probably have been ruled out because of the absence of evidence of cardiac disease which would antedate the formation of an aneurysm, and because there was no expansile pulsation, although the latter would not necessarily have been present. Tumor of the heart would have been more difficult to eliminate. In the absence, however, of disseminated metastases and because there was apparently only a single large lesion, secondary tumor of the heart could have been eliminated. Metastatic carcinoma of the heart occurs only as part of a more or less generalized carcinomatosis and is usually of the small shotty type of lesion. Elimination of this possibility would have been important had the patient's gastric lesion been discovered during the operable stage, since the interpretation of the lesion as a metastatic one might have discouraged surgical intervention.

REFERENCES

- Lauche, A.: Zystenbildung auf der Oberfläche des Herzens nach Perikarditis, *Zentralbl. f. allg. Path. u. path Anat.* 30: 321, 1919.
- Mönckeberg, J. G.: Fremdkörper, Parasiten und Geschwülste. In Henke-Lubarsch's *Handbuch. d. spez. path. Anat. u. Hist.*, Berlin 2: 600, 1924, Julius Springer.
- Perlstein, I.: Sarcoma of the Heart, *Am. J. M. Sc.* 156: 214, 1918.

Department of Reviews and Abstracts

Selected Abstracts

Nuzum, Franklin R., and Elliot, Albert H.: An Analysis of 500 Instances of Arterial Hypertension. *Am. J. M. Sc.* 181: 630, 1931.

Five hundred instances of arterial hypertension, the patients being forty-five years of age or older and having a systolic blood pressure about 150 mm. of mercury are analyzed. Seventy patients with chronic nephritis selected from the above are studied separately. Two hundred and fifty patients in the same age group with an average systolic pressure of 120 mm. of mercury and having only minor noninfectious ailments serve as controls.

Past infections occurred slightly more often in the hypertensive or nephritis groups than in the controls. Acute nephritis and scarlet fever occurred more frequently in the nephritis group than in the 430 remaining hypertensives or in the controls. The incidence of syphilis and typhoid fever was lower than usually reported in hypertension. The number of past infections per patient was nearly identical in each group. All focal infections found in the physical, roentgenographic or laboratory examinations were tabulated for each patient. Head foci were almost evenly distributed among the groups. Focal infection was not the deciding factor in the development of hypertension in these groups.

Obesity was encountered twice as often in the hypertensive patients as in the controls. The average weight for hypertensive group was 10.3 pounds greater than for the control group. Obesity is a contributory factor in the pathogenesis of hypertension. Familial tendency was less important in these series than in other reported studies. A positive history of familial vascular disease was obtained in about 30 per cent in both groups.

Palpable or ophthalmoscopic evidence of arteriosclerosis was found in 17.6 per cent of the main hypertensive group, in 24.2 per cent of the nephritic group and in 14.4 per cent of the control group. Arteriosclerosis of the larger vessels probably has little relation to hypertension.

Olcott, Charles T.: Rupture of a Coronary Artery, Hemopericardium. *New Eng. J. Med.* 204: 760, 1931.

A case of a man of sixty years is presented with pericardial hemorrhage following rupture of the circumflex branch of the left coronary artery. There was an interval of fifteen hours between the admission symptom of precordial pain and death. Atheroma was considered the causative factor.

A review of the literature reveals thirty other cases of rupture of a coronary artery. The etiology of the rupture was not clear in ten cases; in fourteen there were atheromatous changes in the vessels, ten without aneurysm; in five there was an infectious embolism, four of whom had aneurysm; and luetic changes were present with aneurysm in two. There were nineteen males, eleven females and one not stated. The average age of the atheromatous patient was sixty-five; of the infectious 19.2 and of the luetic 46. Rupture occurred in the left artery eleven times; in the right eight times; in both three times and not stated in nine.

Bramwell, Crichton, and Ellis, Reginald: Some Observations on the Circulatory Mechanism in Marathon Runners. *Quart. J. Med.* 24: 329, 1931.

The observations on which this paper is based were made at the last Olympic Games at Amsterdam where the authors examined altogether more than 200 athletes including runners, weight lifters, swimmers, wrestlers and competitors in various other events. The article deals with the findings made by the authors on the cases studied as well as with a discussion of the various principles involved in exercise and the response of the heart to strain and training. It represents a brief well presented discussion of this very important subject and should be of interest to all. They noted that the individuals in the marathon races were inclined to be older, smaller and with a slower pulse rate and a slightly higher blood pressure. They believe that the marathon runner requires a greater stamina which may be found more frequently in older men rather than in younger athletes. They believe that the younger athlete is more inclined to run himself out and to use no caution in conserving his strength. The sprinter is of much less interest than the marathon runner to the cardiologist. His chance of success depends more on perfect neuromuscular coordination. He can run 100 meters without taking a single breath and can trust to the buffering mechanism in his blood and muscles to deal for the moment with all the lactic acid produced. So far as the immediate requirements of his muscles are concerned he might almost dispense with his heart.

For the longer distances on the other hand, the efficiency of the circulatory mechanism is all important; the long distance runner being dependent on the amount of oxygen he can obtain during the race.

The authors discuss all the oxygen requirements and glycogen balance found in athletes of this type. They point out the danger of glycogen death to be found in this group. Two men were on the verge of hypoglycemic convulsions. The use of sugar in the day previous to the race and possibly during the race is based on the utilization of glycogen.

It was found the heart was generally enlarged in marathon runners. The percentage of very large hearts being surprisingly high. They discuss the explanation of the difference that has been found by other workers in this same group. They believe that the recorded instances of small hearts found immediately after the race is due to the position of the diaphragm and to the change in position of the heart rather than to a change in actual size.

Cowan, John: Observations on Angina Pectoris. *Brit. M. J.* 1: 879, 1931.

The author describes various features of angina pectoris from observations on cases under his care. He notes the great variation in the severity of the pain in different patients and describes the site of pain as being generally behind the center of the sternum. The pain often is a feeling of impending dissolution. He notes that angina occurs more commonly in men than in women and most frequently in the fifth and sixth decade; the youngest patient was twenty-three years old. He finds no special relationship between angina and the infections. Rheumatic fever was the most common antecedent in this series but its incidence was small. The association with syphilis is closer. Seventeen patients in the group studied had suffered from syphilis. He believes that muscular anoxemia accounts for the actual attack.

In this series a post-mortem examination was obtained in thirteen cases; of these twelve presented infarcts or fibrosis of the muscles, the coronary arteries being extensively diseased. In two cases there was rupture of the heart. Vasomotor disturbances not infrequently accompanied the attacks. The association between angina and the excessive use of tobacco is well established.

Treatment depends on the etiology in the particular case. In cases due to coronary disease every endeavor should be made to prevent undue strain on the heart until satisfactory anastomoses have had time to form and to supply the myocardium with sufficient blood. The treatment of a paroxysm is necessary but of less importance than its prevention. Angina is a danger signal, a sign of some harmful activity, and if we make the patient insensitive to his discomforts he will soon kill himself. For this reason surgical treatment while satisfactory to relieve pain should not be resorted to except in extreme cases.

McEachern, Donald, and Rake, Geoffrey: A Study of the Morbid Anatomy of Hearts from Patients Dying with Hyperthyroidism. *Bull. Johns Hop. Hosp.* 48: 273, 1931.

This study has been made on all the cases of hyperthyroidism coming to autopsy in the Johns Hopkins Hospital since its opening in 1889. Thirty-seven cases were found in which there was conclusive evidence that hyperthyroidism existed. Ten cases were discarded because tissues or sections were not available. Twenty-five control cases were selected according to age for each of the six decades in which the cases of hyperthyroidism were scattered. These 150 cases were chosen consecutively from the autopsy records. Fourteen hearts of the total series showed no changes of the kind or degree not to be found in the control groups of similar age or which are not well recognized as occurring in general autopsy material in the absence of specific heart disease. In eight instances moderate perivascular or intermuscular fibrosis or small round cell infiltration was found. Similar changes were also encountered among the control cases though less frequently.

Conspicuous alterations were found in five instances; in three of which there was coexistent heart disease. Cardiac hypertrophy was noted in 16 of the 27 cases. No relationship could be established between the coincidence of auricular fibrillation or the duration of hyperthyroidism and the ultimate findings in the heart. Congestive heart failure occurred in five of the six cases that presented coexisting organic heart disease.

The authors believe that from this evidence it is impossible to ascribe the cardiac phenomena to structural changes in the muscle. It is pointed out that the heart from hyperthyroid animals continued to beat when isolated at a much faster rate than similar preparations from normal animals. Emphasis is placed on the desirability of studying the problem from the viewpoint of metabolic and functional alterations in the myocardium.

Carter, Edward P., and Baker, Benjamin M., Jr.: Certain Aspects of Syphilitic Cardiac Disease. *Bull. Johns Hopkins Hosp.* 48: 315, 1931.

The authors have undertaken a study of the cases of syphilitic aortic disease, aortitis, aortic insufficiency either alone or combined with aneurysm and of aneurysm alone, admitted to the wards of the Johns Hopkins Hospital since 1910 at which time the Wassermann test came into accepted use. They have completed a detailed analysis of the first 100 cases. This has been supplemented by the pathological findings in those cases that came to autopsy. Their determinations are based chiefly on this series together with certain additional clinical material including statistical figures of the remaining cases of the entire series of 367. They have found the increased incidence of syphilis in colored patients, being about three times more frequent in colored males than in white males. They believe that every individual having a syphilitic infection is a potential subject of cardiovascular disease. What constitutes the predisposing factor which determines the peculiar arterial invasion with the ultimate involvement of the aortic ring or the development of an aneurysm is not clearly understood.

The question as to why the coronary artery escapes a similar fate has not been satisfactorily answered.

The Wassermann reaction was positive in an extremely high percentage of cases. Latent period from the day of the primary lesion to the first appearance of subjective symptoms was fifteen years and five months; two extremes being three years and thirty-nine years. Various symptoms are discussed. It was noted that auricular fibrillation was entirely absent in this series of 100 cases. Treatment of these patients is discussed and an extensive bibliography is included in the article.

Raab, W.: Central Vasomotor Irritability. Contribution to the Problem of Essential Hypertension. Arch. Int. Med. 47: 727, 1931.

In decerebrate cats with the vagi cut, the following experimental results were obtained:

1. There was a strong increase of the arterial blood pressure for a period up to two hours by the continuous perfusion of the brain stem with blood containing abnormally high amounts of lactic acid.

2. Hyperirritability of the vasomotor centers resulted under the influence of a shortage of oxygen or perfusion with lactic acid, or with the injection of lactic acid into the suboccipital cavity. The inhalation of carbon dioxide causes a considerably greater rise and the hyperventilation a greater fall in blood pressure under these conditions than occur under normal conditions.

3. Sensitive stimuli cause higher rises of blood pressure during the conditions mentioned than they do normally.

4. The effect of epinephrine is considerably weakened and inverted during the lack of oxygen; it is scarcely altered during perfusion with lactic acid.

5. Acetic acid increases the irritability of the vasomotor center in the same way as lactic acid; alkali gives irregular effects.

6. These experimental results correspond to the following characteristic features of essential hypertension: (1) High blood pressure; (2) hypersensitivity to the inhalation of carbon dioxide (abnormal increase of blood pressure) and to hyperventilation (abnormal fall of blood pressure); (3) hypersensitivity to peripheral sensitive stimuli; and (4) weakened or inverted effect of epinephrine.

7. The conclusion was reached that the symptoms of essential hypertension can be considered due to the local need of oxygen and the accumulation of lactic acid within the vasomotor centers of the brain stem as a consequence of local circulatory disturbances. The actual level of the blood pressure in hypertension would accordingly be composed of the sum of the stimulus through lactic acid plus the pathologically increased responses to the stimulus of the normal carbon dioxide tension of the blood and of different kinds of sensitive and emotional stimuli.

Ayman, David, and Pratt, Joseph H.: Nature of the Symptoms Associated with Essential Hypertension. Arch. Int. Med. 47: 675, 1931.

The possibility of a psychic origin for the early symptoms associated with essential hypertension was suggested by the clinical experiments of one of the authors. This idea was further encouraged by an earlier study in which 82 per cent of 40 hypertensive patients were definitely relieved of their symptoms by suggestion. Added support for this opinion was afforded by the widespread belief that as in psychoneuroses, the greater relief from the symptoms of which hypertensive patients complain may be obtained by the removal of worries, fears and other disturbances in the psychic sphere. The cause of this similarity, the problem of the relation of the symptoms presented by hypertensive patients to those observed in the psychoneuroses, seemed worthy of study.

This study has consisted of noting the symptoms associated with essential hypertension and those of the psychoneuroses. It was found that the early symptoms could not be differentiated between the two conditions either by their incidence or by their general and individual characteristics; that in both groups of patients no abnormality on physical or laboratory examination could be found adequate to explain the symptoms and finally that in both groups of patients a significant degree of maladjustment of emotional difficulties was found to explain the development of symptoms at the time they appeared. Additional evidence that the early symptoms associated with essential hypertension are due not to organic changes but to the emotional maladaptation of the patient can be noted in the results of treatment. While it seems reasonable to conclude that the early symptoms associated with essential hypertension are probably of psychic origin, the fundamental mechanism is not clear. Constitutional influences, endocrine products and possibly other factors may contribute to lessen the hypertensive patients psychic and physical capacity for withstanding the stress and strain of life.

Wishnofsky, Max, and Byron, Charles S.: Carbohydrate Metabolism in Hypertension. *Arch. Int. Med.* 47: 790, 1931.

A dextrose tolerance test was performed on 10 patients suffering from hypertension. The blood sugar and the respiratory quotient curves were studied simultaneously. In six of the ten cases the blood sugar during fasting was higher than normal. It was shown that all patients with hypertension have high blood sugar curves. The respiratory quotient curves were normal in nine of the ten cases. This is adequate proof that there is no diminution in the secretion of insulin in hypertension and that these patients are neither potentially nor mildly diabetic. It disproves the theory that the disturbance in carbohydrate metabolism in hypertension is caused by sclerosis of the blood vessels of the pancreas. In the case in which the respiratory quotient curve was lower than normal diabetes mellitus independent of the hypertension could be considered to exist.

The theory that hyperadrenalemia is the cause of the disturbance cannot be proved in the present state of knowledge.

The mechanism concerned in producing this disturbance in carbohydrate metabolism is unknown and awaits further research for its elucidation.

Boswell, Clarence H., and Palmer, Harold D.: Progressive Thrombosis of the Pulmonary Artery. *Arch. Int. Med.* 47: 799, 1931.

The authors report a case of a man aged thirty-nine years who had definite symptoms for some time prior to death which suddenly became aggravated and terminated fatally in a relatively short time. Post-mortem examination revealed thromboarteritis of the pulmonary artery with complete occlusion. The ante-mortem diagnosis had been myocardial injury. The thrombus at post-mortem seemed to be of some age, being well organized and in places canalized; though old, the thrombus became complete only during the last few hours as is shown positively by the newer portions of the thrombus. The thrombus on the left side was much less extensive and probably the result of right-sided retrogression. There was no evidence of chronic congestion showing that the heart was competent up to the time of the last sudden occlusion.

The authors suggest this to be a case of thromboarteritis in the pulmonary artery and not embolic. The sequence of events may have been: (1) acute respiratory infection occurring five weeks before death resulting in (2) lymphadenitis and bronchitis; this infection extended into the pulmonary artery as (3) an arteritis. The high coagulability of the venous blood in the pulmonary artery accompanying

the sepsis, together with a low blood pressure slowing the stream over a damaged artery lining, produced (4) a thrombus which was not extensive enough to cause death at that time. Later, after a good night's rest with slowing of the blood stream during sleep (5) another thrombus formed and the symptoms appeared with the activity on awakening. (6) Death did not occur until the new portion had retrogressed far enough to occlude the larger pulmonary branches.

Had this patient lived longer the complete syndrome on which the diagnosis of Ayerza's disease could be made might have developed; hypertrophy of the right side of the heart from the extra work thrown on it; polycythemia from the demand for more oxygen carriers; sclerosis of the pulmonary artery; chronic cough; cyanosis and later serious cardiac failure.

Sutton, Lucy Porter, and Wyckoff, John: Digitalis. Its Value in the Treatment of Children with Rheumatic Heart Disease. Am. J. Dis. Child. 41: 801, 1931.

Twenty-five cases of digitalization in twenty-two patients with heart failure associated with active rheumatic heart disease under controlled conditions, digitalis of known biologic activity being used, are reported. In twenty-four digitalizations of twenty-one children, the average calculated dose necessary to produce the effect of digitalis was 0.15 cat units per pound of body weight. All of these patients showed some improvement in the signs of heart failure when fully digitalized. It was possible to produce the effect of digitalis without producing toxic symptoms in the majority of cases.

The authors conclude that digitalis is of value in the treatment of children with heart failure. It is effective in doses comparable to those required by adults without necessarily producing intoxication. It is effective in the presence of active infection of the heart.

Blackford, L. Minor, and Hoppe, Lewis D.: Functionally Two-Chambered Heart. Am. J. Dis. Child. 41: 1111, 1931.

A case of an infant aged six and one-half months is reported with clinical, laboratory and post-mortem observations. The right atrium opened through the foramen primum into the left atrium which in turn opened through the mitral valve into a single ventricle. The tricuspid valve was absent. A small right ventricle in the mass of ventricular muscle between the stenosed opening in the interior wall of the large ventricle and a second stenosis at the beginning of the bulbus cordis was revealed on detailed dissection. The aortic valve was normal though the pulmonic valve was bicuspid. Extreme stenosis of the ventriculobulbar junction prevented the passage of an adequate amount of blood to the lungs. A theory is advanced to explain the changes in circulation that occurred in this patient.

Blumgart, Herrman L., Lawrence, John S., and Ernstene, A. Carlton: The Dynamics of the Circulation in Coarctation (Stenosis of the Isthmus) of the Aorta of the Adult Type. Arch. Int. Med. 47: 806, 1931.

Coarctation of the aorta presents an opportunity to compare in the same person the dynamics of the circulation in arterial hypertension above the point of constriction with the dynamics of blood flow under lower pressure below the level of the stenosis. The results of an extensive study of two patients with coarctation of the aorta are presented.

The diagnosis of coarctation of the aorta was corroborated at necropsy in both patients.

The diagnosis was established in both patients by (1) arterial hypertension in the arms as contrasted with the relatively low blood pressure in the legs; (2) evidence of extensive collateral arterial circulation observed on physical examination and also made apparent by the erosions of the ribs seen in the roentgenograms of the chest; and (3) diminution and retardation of the arterial pulses in the legs.

Although arterial hypertension presumably had been present above the level of the coarctation in both patients for over forty years, physical examination and roentgenographic studies failed to disclose any perceptible difference in the degree of arteriosclerosis in the upper and lower parts of the body.

The arteriolar blood pressure in the arms was normal. This suggests that while increased peripheral resistance may, as in essential hypertension, be responsible for the arterial hypertension above the coarctation, this increased resistance is due not to increased arteriolar resistance but rather to the resistance offered by the constricted aorta and the collateral pathways.

The velocity of blood flow in the larger arteries of the leg was reduced and the arterial-arteriolar difference in blood pressure was greatly diminished. According to the measurements of oxygen in the blood, the blood supply to the tissues under resting conditions was nevertheless within the limits of normal.

The hypothesis that the small arterial-arteriolar difference in the local circulatory reserve is discussed. This condition is contrasted with that above the level of the coarctation where a marked difference in arterial-arteriolar pressure prevails.

Considerations are brought forward that suggest that symptoms of local circulatory insufficiency in the legs such as intermittent claudication and nocturnal cramps may be the earliest indication of a failing heart in patients with coarctation of the aorta and should call for effective treatment, even before the appearance of dyspnea or any other evidence of circulatory stasis.

Morton, John J., and Scott, W. J. Merle: *Methods for Estimating the Degree of Sympathetic Vasoconstriction in Peripheral Vascular Diseases*. New Eng. J. Med. 204: 955, 1931.

The authors have studied the surface temperature changes in suitable locations following the various types of anesthesia, both general anesthesia, spinal anesthesia and local anesthesia produced by anesthetizing peripheral nerves. They have studied both the methods of estimating surface temperature, the variations which may be found, and the errors which occur in these different types of anesthesia.

They believe that the number of degrees by which a given case fails to attain the lower limits of the normal vasodilatation level is of much more value in estimating the proportion of spasm and occlusion than the number of degrees through which the surface temperature rises. This is a point of particular importance in the management and prognosis of many of the cases of common vascular disease in the extremity.

Book Reviews

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. III Tagung. Theodor Steinkopff, Dresden and Leipzig, 1930. Pp. 150.

The papers and discussions collected here were presented at a meeting held in Dresden on June 11 and 12, 1930. The presentations are concise and the illustrations carefully prepared. The volume is of special value to those who wish to keep in touch with recent work in other countries and it is interesting to note the subject matter of the papers. There are papers on venous pressure and on changes in the peripheral circulation in hypertension, microphotographic studies of the capillaries, notes on respiration and chemical studies in relation to the circulation and respiration. The opening addresses are by Dr. Bürker (Giessen) on the red cells and by Dr. Lindhart (Copenhagen) on technical methods for the clinical study of problems of the circulation.

E. H.

DIE REFLEKTORISCHE SELBSTSTEUERUNG DES KREISLAUFES. By Dr. Eberhard Koch. Theodor Steinkopff, Dresden and Leipzig, 1931. Pp. 234 with 44 illustrations.

This is the first of a series of monographs entitled "Ergebnisse der Kreislaufforschung" edited by Bruno Kisch. It is devoted entirely to a consideration of the aortic (depressor) nerve (Coyn and Ludwig) and the sinus nerve (Hering and De Castro), and their receptors in the arch of the aorta and in the carotid sinus respectively. Because changes in heart rate and in peripheral vessel muscle tone are reflexly caused by changes of arterial pressure in the aorta and in the carotid sinus, Koch calls this mechanism "the pressor receptor mechanism of the circulation." Through this system the relative stability of blood pressure and heart rate is maintained. Neither the physical, chemical or hormonal changes in the blood, which undoubtedly play a part in the regulation of the circulation, nor the peripheral vasomotor mechanism are discussed.

In Part I the embryology, anatomy and comparative anatomy of this pressor receptor system are given and the literature is discussed. Of particular interest in this part is the description of the recent anatomical studies by De Castro on the sinus nerve and its receptors in the carotid sinus.

In Part II is found a complete résumé of the literature and a discussion of the normal and pathological physiology and the pharmacology of both the aortic depressor and the carotid sinus systems. It is based particularly upon studies of Hering, De Castro, and Heymans and some corroborative studies by the author. The importance of this section can be judged by the statement that a permanent denervation of the carotid sinus and the aorta will cause in experimental animals a permanent hypertension and that it is probably common in human beings to have an hypertension on such a basis. The effect of stimulation of the aortic and carotid sinus nerve on respiration, intestinal peristalsis, tonus of skeletal muscles and upon the function of organs of internal secretion is briefly discussed.

In Part III the author describes a method of changing and measuring the endo-arterial pressure in the carotid sinus. By this method he has been able to study quantitatively the reflex blood pressure and heart rate changes. The results of these experiments are fully discussed.

This monograph is a very well written and well illustrated work in which a newer and epoch-making concept of the physiology of the circulation is described. It is a treatise that should be read and studied not only by physiologists and anatomists, but since this newer physiology may change our present concept of diseases like hypertension, etc., it should be read and thoroughly digested by every practitioner in internal medicine.

C. S.

CLINICAL ELECTROCARDIOGRAPHY. By Sir Thomas Lewis. Ed. 5, London, Shaw and Sons, 1931.

The fifth edition brings this authoritative guide to the study of electrocardiography up to date without changing the character of the volume. It remains a small handbook of clinical electrocardiography, the result of years of experience compressed within 120 pages, and it needs no introduction to those who are familiar with the earlier editions or with the other writings of Sir Thomas Lewis.

E. H.

OCLUSION CORONARIA, BRUSCA Y LENTA. By T. Padilla and P. Cossio. El Ateneo, Buenos Aires, 1930.

In a richly illustrated volume of some 225 pages the Argentinian authors offer a clear and logical presentation of the subject of coronary occlusion. The first half of the book is devoted to a consideration of the anatomy and physiology of the heart and its circulation and of the pathological and etiological factors in coronary artery disease. In the second half the clinical aspects of coronary closure, both

sudden and gradual, are presented in a form which is simple and concise and yet is reasonably comprehensive. The numerous illustrations are clear and easily understood and contribute much to the value of the text. The bibliography is adequate and well chosen but is open to the criticism that frequently the same reference appears two or three times.

L. A. C.

The American Heart Journal

VOL. VI

AUGUST, 1931

No. 6

Original Communications

OCCURRENCE AND SIGNIFICANCE OF ELECTROCARDIOGRAMS DISPLAYING LARGE Q-WAVES IN LEAD III*

FREDRICK A. WILLIUS, M.D.
ROCHESTER, MINNESOTA

IN A RECENT publication, Pardee² called attention to electrocardiograms exhibiting large Q-waves in Lead III, and found that 63 per cent of the forty-three patients in his group had the anginal syndrome. The possibilities of this observation prompted me to carry out an investigation in a larger series of cases.

MATERIAL

The electrocardiograms in the files at The Mayo Clinic were carefully searched, and in approximately 70,000 records, 300 tracings were found which conformed to the criteria demanded by Pardee. The incidence of the electrocardiograms with large Q-waves in Lead III cannot be accurately established, owing to the fact that many tracings that previously had been considered to be essentially normal had been destroyed. It is possible that among these were some with large Q-waves in Lead III.

Pardee made his selection on the following grounds: (1) Electrocardiograms of left axis deviation, or normal axis deviation, were chosen; those of right axis deviation were excluded, for in these Q_s is normal; (2) the excursion of the Q-wave in Lead III was more than 25 per cent of the greatest excursion of the QRS complex in any lead; (3) records with notching deformity of the QRS complex in Lead III, the so-called W and M complexes, were excluded; and (4) in all records chosen there was, in Lead III, an initial downward deflection (Q), succeeded by a definite upward deflection (R) and no S-wave.

These criteria were rigidly adhered to in the selection of my cases. Pardee investigated the incidence of these electrocardiograms as they may be found in examination of persons whose hearts are apparently normal, and found only two such records in 277 such cases, an inci-

*From the Section on Cardiology, The Mayo Clinic.

dence of only 0.7 per cent. In discussing the occasional occurrence of a large Q-wave in Lead III in electrocardiograms of apparently normal hearts, he suggested the possibility of unusual distribution of the branches of the auriculoventricular bundle, and that a high diaphragm may contribute to the appearance of this abnormally large Q-wave. In The Mayo Clinic series of 300 cases in which there were large Q-waves in Lead III only three patients (1 per cent) with apparently normal hearts were found. Wolferth,³ in studying the electrocardiograms of 700 normal subjects, did not find any instance of a large Q-wave in Lead III. Later in this paper the material studied by Pardee, and that studied by Wolferth will be employed as a composite, control group of 977 normal persons.

CLINICAL CORRELATION

The correlation of the electrocardiograms under consideration with the clinical diagnoses in my series differed somewhat from that of Pardee. The greatest incidence of the characteristic electrocardiographic changes occurred in cases of hypertensive heart disease; that is, of the 300 characteristic electrocardiograms, 120 (40 per cent) were obtained in cases of this type (Table I). The anginal syndrome without hypertension occurred in 76 cases or 25.3 per cent of those which gave the characteristic electrocardiogram, and hypertensive heart disease, associated with the anginal syndrome, in 39 cases (13 per cent). Arteriosclerotic heart disease, without the anginal syndrome and without hypertension, occurred in 33 cases (11 per cent).

TABLE I

CORRELATION OF LARGE Q-WAVES IN LEAD III WITH CLINICAL CONDITIONS IN 300 CASES

| CLINICAL DIAGNOSIS | CASES | PER CENT |
|--|-------|----------|
| Hypertensive heart disease | 120 | 40.0 |
| Anginal syndrome | 76 | 25.3 |
| Hypertensive heart disease with anginal syndrome | 39 | 13.0 |
| Arteriosclerotic heart disease without anginal syndrome | 33 | 11.0 |
| Total | 268 | 89.3 |
| Exophthalmic goiter | 8 | 2.8 |
| Syphilitic aortitis with aortic insufficiency | 7 | 2.3 |
| Rheumatic heart disease: | | |
| mitral stenosis | 5 | 1.7 |
| aortic stenosis | 3 | 1.0 |
| Chronic pericarditis with adhesions | 1 | 0.3 |
| Congenital heart defect; probably patent ductus arteriosus | 1 | 0.3 |
| Enlarged heart of undetermined origin | 1 | 0.3 |
| Arteriosclerotic disease of vessels of leg | 1 | 0.3 |
| Exertion dyspnea without clear evidence of cardiac disease | 2 | 0.7 |
| Apparently normal heart | 3 | 1.0 |
| Total | 32 | 10.7 |

In the three groups, in which there was clinical evidence of coronary disease, there were 148 cases (49.3 per cent of 300). For comparison,

Pardee's data are presented in Table II where it is seen that the anginal syndrome occurred in 27 cases (63 per cent). Pardee speculated on the possibility of narrowing of the coronary arteries having taken place in 8 other cases (18 per cent); thus, he considered the theoretical possibility that coronary disease was present in 81 per cent of his cases.

TABLE II

CLINICAL CORRELATION OF LARGE Q-WAVES IN LEAD III WITH CLINICAL CONDITIONS IN FORTY-THREE CASES (PARDEE)

| CLINICAL DIAGNOSIS | CASES | PER CENT |
|---|-------|----------|
| Anginal syndrome | 27 | 62.8 |
| Syphilitic aortic insufficiency | 1 | 2.3 |
| Myocardial fibrosis: | | |
| with congestion | 4 | 9.4 |
| with arrhythmia | 1 | 2.3 |
| Rheumatic heart disease: | | |
| active, with mitral insufficiency | 1 | 2.3 |
| aortic insufficiency, with or without mitral disease | 2 | 4.7 |
| mitral insufficiency | 0 | 0.0 |
| mitral stenosis, with or without mitral insufficiency | 1 | 2.3 |
| Arteriosclerosis with hypertension | 1 | 2.3 |
| Hypertension with arrhythmia | 1 | 2.3 |
| Hyperthyroid (enlarged) heart; enlargement determined by percussion and roentgenograms; patient aged 54 years | 1 | 2.3 |
| Pregnancy; a record after delivery did not show a large Q ₂ (normal heart) | 1 | 2.3 |
| Effort syndrome, including the group of cases showing neurocirculatory asthenia (normal heart) | 2 | 4.7 |
| Normal heart | 0 | 0.0 |
| Congenital heart defect | 0 | 0.0 |
| Arteritis obliterans | 0 | 0.0 |

It is possible of course that in some of the cases that I have classified as examples of hypertensive heart disease there may have been associated coronary disease, for relatively high coexistence of these conditions is seen at necropsy. However, critical review of these records did not justify a classification other than that given. It may be noted that the four groups embodying hypertensive and arteriosclerotic heart disease, combined, include 268 cases (89.3 per cent of the entire 300).

In analyzing the remaining thirty-two cases (10.7 per cent) of the series, a rather varied aggregation of conditions is found (Table I). Considering the predominant influence of these conditions on the ventricles it becomes evident that the majority of disorders exerted strain on the left ventricle (20 cases, 6.6 per cent of 300). It is even possible that the remaining 9 pathological conditions (mitral stenosis, congenital cardiac defect, enlarged heart of undetermined origin, and dyspnea on exertion without clear-cut evidence of cardiac disease; Table I) were complicated by lesions that likewise produced strain predominantly on the left ventricle.

TABLE III

| CLINICAL DATA | | ELECTROCARDIOGRAM | DATA OBTAINED AT NECROPSY | |
|---------------|---|--|---------------------------|--|
| AGE AND SEX | DIAGNOSIS | | WEIGHT OF HEART, GM. | PATHOLOGICAL FEATURES |
| 56 M | Anginal syndrome | Sinus arrhythmia; negative T-wave Lead I, depressed R-T segment Leads I and II; elevated R-T segment Lead III | 395 | Advanced, generalized arteriosclerosis with sclerosis of the coronary arteries and myocardial fibrosis |
| 54 M | Coronary thrombosis with cardiac infarction; essential hypertension | Sinus rhythm; negative T-waves in Leads I and II; R-T segment depressed in Leads I and II and elevated in Lead III | 420 | Coronary sclerosis with thrombotic occlusion; infarction of left ventricle and mural thrombosis |
| 53 M | Hypertensive heart disease with anginal syndrome | Sinus rhythm; negative T-wave Lead I; R-T segment depressed in Lead I and elevated in Lead III | 662 | Marked coronary sclerosis and cardiac hypertrophy; mural thrombosis of right ventricle |
| 58 M | Hypertensive heart disease | Sinus rhythm; negative T-wave in Lead III | 550 | Cardiac hypertrophy |
| 60 F | Hypertensive heart disease | Sinus rhythm; negative T-wave in Lead III | 385 | Cardiac hypertrophy |
| 62 M | Hypertensive heart disease | Sinus rhythm; negative T-wave Lead III; R-T segment depressed in Leads I and II; elevated in Lead III | 400 | Cardiac hypertrophy |
| 67 M | Arteriosclerotic heart disease | Sinus rhythm | 290 | A few small epicardial hemorrhages; moderate calcification at the base of the right and left coronary cusps of the aortic valve; slight sclerosis of the coronary arteries and moderate sclerosis of the aorta; patent foramen ovale |
| 36 F | Syphilitic aortitis with aortic insufficiency | Sinus rhythm; negative T-wave in Leads I and II | 400 | Marked syphilis of the aorta with enormous dilatation of the left ventricle |
| 52 M | Chronic endocarditis with aortic insufficiency; anginal syndrome | Sinus rhythm; diphasic T-waves in Leads I and II; negative T-wave in Lead III | | Chronic aortic endocarditis with insufficiency; cardiac hypertrophy and dilatation; aortitis (syphilitic?) with fusiform aneurysm of ascending aorta; coronary sclerosis |

Data Obtained at Necropsy.—Only 9 cases were available in which pathological study of the hearts was carried out. The detailed data are shown in Table III. This group is obviously too small to permit definite conclusions, although certain facts are clearly portrayed. In 8 cases, the hearts were definitely hypertrophied, ranging in weight from 385 to 700 gm. Three cases of hypertensive heart disease occurred without associated involvement of the coronary arteries. This lends support to the conception that the dominant condition is hypertensive heart disease, as is brought out in Table I. Four cases presented the anginal syndrome, and five cases presented well-marked evidence of coronary disease. In all the cases there was evidence of disease of the left ventricle.

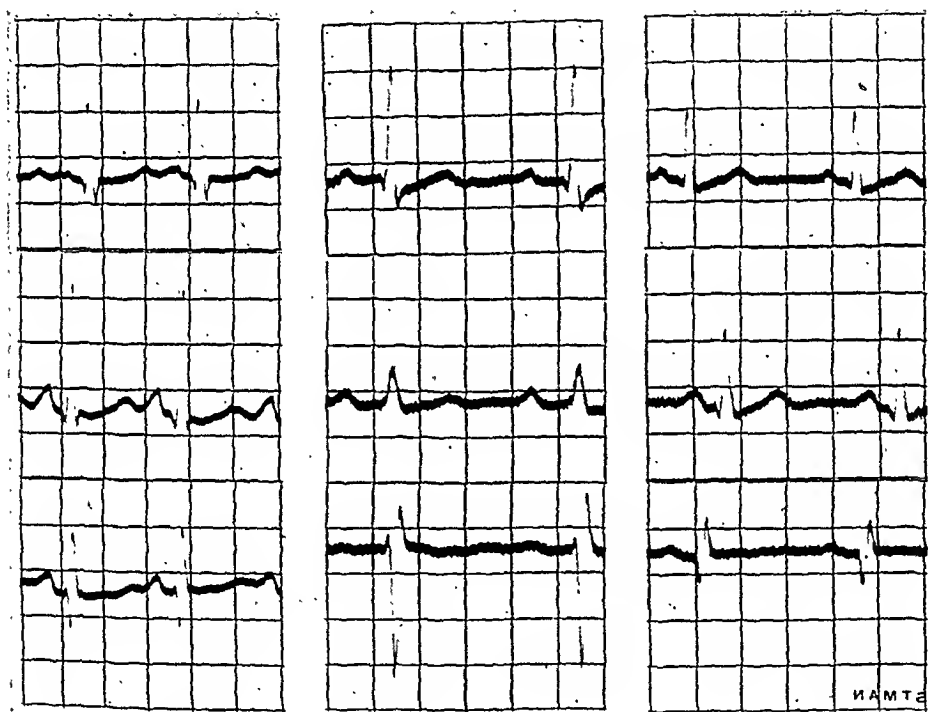


Fig. 1.—Electrocardiograms which contain large Q-waves in Lead III.

DATA ON CONTROL SERIES

The composite group^{2, 3} of electrocardiograms, made from 977 normal persons, revealed only two cases (0.2 per cent) in which there were large Q-waves in Lead III. This extremely low incidence is of considerable significance. In order to obtain further control data as to the incidence of these electrocardiograms in cases of cardiac disease I took records, in each of which the cardiac condition corresponded, as nearly as possible, to one of the four conditions which were seen most frequently in my series of 300 cases. This selection was made without knowledge of the nature of the electrocardiograms. Of 120 cases of hypertensive heart disease thus chosen, in twelve (10

per cent) there were large Q-waves in Lead III. Large Q-waves in Lead III occurred in five cases (7 per cent) of seventy-six cases in which the anginal syndrome was present, in four cases (10 per cent) of thirty-four cases of hypertensive heart disease with the anginal syndrome, and in one case (3 per cent) of thirty-three cases of arteriosclerotic heart disease without the anginal syndrome and without hypertension.

ASSOCIATED ELECTROCARDIOGRAPHIC FEATURES IN THE SERIES OF 300 CASES

In the majority of records (214 cases, 71.4 per cent of 300) the direction of the T-waves was normal. That is, they were upward in all leads in eighty-eight cases (29.4 per cent of 300) and upright in Leads I and II and downward in Lead III in 126 cases (42 per cent of 300). This incidence is slightly greater than that found by Pardee (63 per cent).

TABLE IV
ASSOCIATED SIGNIFICANT T-WAVE NEGATIVITY

| T-WAVE NEGATIVITY | PARDEE SERIES | | WILLIUS SERIES | |
|---------------------|---------------|----------|----------------|----------|
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Lead I | 1 | 2.5 | 28 | 9.3 |
| Leads I and II | 4 | 9.0 | 20 | 6.6 |
| Leads II and III | 11 | 25.0 | 27 | 9.0 |
| Leads I, II and III | 0 | 0.0 | 11 | 3.7 |
| Total | 16 | 37.2 | 86 | 28.6 |

The incidence of significant T-wave negativity is shown in Table IV, and is there compared with the observations of Pardee. The occurrence of T-wave negativity according to leads in my series varies considerably from that of Pardee, particularly as far as Leads II and III are concerned. He stated that the greater frequency of inversion of T-2 and T-3 (25 per cent) as compared with T-1, with or without T-2 (11.5 per cent) is noteworthy. In my series, however, this ratio is reversed; T-wave negativity in Leads II and III occurred in only 9 per cent of the cases, whereas 19.6 per cent of the cases displayed T-wave negativity in Lead I, Leads I and II and in all leads. These ratios are in accord with the conception that there was strain predominantly on the left ventricle, as already mentioned, and conform to the views of Barnes and Whitten¹ regarding T-wave negativity independent of cardiac infarction.

The only other significant electrocardiographic features encountered in my series were in eighteen cases (6 per cent of 300) of auricular fibrillation. Two of these cases were associated with T-wave negativity in Leads II and III.

Thus, in the complete group of 300 cases, the only significant electrocardiographic feature in 198 cases (66 per cent) was the large Q-wave in Lead III. Therefore, this abnormality may be looked on as being an additional diagnostic sign that may be of reliable significance

when the electrocardiogram is otherwise unaltered. It appears to occur predominantly in diseases exerting their influence chiefly on the left ventricle, but insufficient reports of necropsy are available at this time to permit definite conclusions to be formed. Although the anginal syndrome occurred frequently (38.3 per cent) when this form of electrocardiogram was present, it was by no means limited to cases of which the anginal syndrome was a feature.

SUMMARY

Three hundred cases in which there were electrocardiograms with large Q-waves in Lead III, according to the criteria of Pardee, are presented. The majority of these records (268 or 89.3 per cent) were obtained in examination of patients who had one of the following conditions: hypertensive heart disease, the anginal syndrome, hypertensive heart disease accompanied by the anginal syndrome, or arteriosclerotic heart disease not accompanied by the anginal syndrome or hypertension. The remaining thirty-two patients (10.7 per cent) had miscellaneous conditions, but the majority of them had diseases that exert their influence chiefly on the left ventricle. Only three cases (1 per cent) in which the patients apparently had normal hearts were found. In 198 cases (66 per cent of 300) the large Q-wave in Lead III was the only significant electrocardiographic feature present, permitting the conclusion that this abnormality may be considered as an additional diagnostic sign. In the composite group of 977 normal persons studied by various observers there were only two cases (0.2 per cent) in which large Q-waves occurred in Lead III.

REFERENCES

1. Barnes, A. R., and Whitten, M. B.: Study of T-Wave Negativity in Predominant Ventricular Strain, *AM. HEART J.* 5: 14, 1929.
2. Pardee, H. E. B.: The Significance of an Electrocardiogram With a Large Q in Lead III, *Arch. Int. Med.* 46: 470, 1930.
3. Wolfert, C. C.: Personal communication to the author.

THYROTOXIC CIRCULATORY SYMPTOMS WITH LOW METABOLIC RATE*

ROGER S. MORRIS, M.D.
CINCINNATI, OHIO

HYPERTHYROIDISM is one of the well recognized causes of heart disease. In the earlier stages, sinus tachycardia is the commonest disturbance of the circulation. Auricular flutter is encountered at times, as electrocardiographic records have demonstrated. In the later stages of hyperthyroidism, auricular fibrillation and congestive heart failure are frequently seen. If the damage to the myocardium has not been too great, the fibrillation may cease following subtotal thyroidectomy.

In frank hyperthyroidism with increase in the metabolic rate, the recognition of the nature of the circulatory disturbance is not difficult. In the case of "masked" hyperthyroidism, however, painstaking study of the case is required to bring out the underlying thyroid factor, as Levine,¹ Hamburger and Lev² and others have shown. Levine considers transient auricular fibrillation the most characteristic manifestation. The heart sounds are peculiarly loud and hyperactive. Failure to obtain the usual reduction in rate through digitalization is suggestive. Increase in the metabolic rate, combined with such data as the general appearance of the patient; greater comfort in cold weather than in warm; brief attacks of diarrhea and vomiting; alert, quick movements; often a peculiar stare to the eyes and a tremor of the fingers; transient glycosuria—all of these, with increased basal metabolic rate, in the absence of exophthalmos or obvious goiter, lead to the diagnosis. Coexisting organic heart disease renders the diagnosis even more difficult. Levine found complete relief or marked improvement following subtotal thyroidectomy. Hamburger and Lev discuss hyperthyroidism masked by congestive heart failure, by anginal heart failure, associated with organic heart disease of rheumatic or arteriosclerotic type, or masquerading as diabetes mellitus or as pernicious hyperemesis.

Cases in every way similar but with a low metabolic rate may be encountered, as we have reported elsewhere.³ With increasing experience, we are finding the condition much more frequently, and believe that early recognition with operation is of great importance.

The evidence of circulatory disturbance may not be striking in some instances, as the first of the following cases illustrates.

*From the Department of Internal Medicine, University of Cincinnati.

CASE 1.—R. E. M., male, aged 34 years, was admitted to the hospital November 17, 1930, for the treatment of duodenal ulcer which had caused a rather severe hematemesis. He was placed on the Sippy treatment and improved satisfactorily, but complained of a nervous tension and of palpitation. It was noted that there was a slight stare and lid-lag but no exophthalmos. There was no visible goiter, but palpation revealed a moderately enlarged adenomatous gland, over which a faint continuous murmur was audible. There was an instability of the pulse, the rate being between 90 and 100. There was a strong pulsation in the abdominal aorta. The blood pressure was increased, averaging between 160/80 and 170/90 mm. The heart action was forceful. Relative dullness measured 2×9 cm. The sounds were loud and clear, the rhythm was regular. There was a weak systolic shock at the apex. There was slight fine tremor in the fingers. The skin was of normal texture and moist. The remainder of the physical examination was negative. On November 17, the basal metabolic rate was -17 per cent; on November 24 the rate was -32 per cent; on November 29 a third determination also gave a rate of -32 per cent. Differential count showed 27 per cent lymphocytes. Subtotal thyroidectomy was performed December 3. A fairly large adenomatous gland was found. For two days after operation thyrotoxic symptoms increased but were controlled by luminal and by increasing the dose of Lugol's solution, which had been started prior to operation. Thereafter the patient made an uneventful recovery. Nine days after operation the basal metabolic rate was -12 per cent. A month after operation the metabolic rate was -10 per cent, the pulse rate was normal and the blood pressure 120/80 mm. The nervousness and palpitation disappeared and the patient was feeling perfectly well.

This case represents a mild form of thyrotoxic circulatory disturbance. Palpitation, consciousness of the heart's action and tachycardia were the only symptoms referable to the circulation. There was nervousness and a tendency to perspire. Physical findings indicating thyrotoxicosis were the lid-lag and stare, goiter, tremor of the fingers, overactive heart with loud sounds, moderate tachycardia, and increase in the pulse pressure. The basal metabolic rates would seem to exclude a hyperthyroidism, yet the symptoms and physical signs which suggested a mild thyrotoxicosis cleared up after subtotal thyroidectomy just as in cases of hyperthyroidism. Three weeks of absolute bed rest prior to operation had been of no avail. The findings in no way suggested hypothyroidism. The metabolic rate rose to the lower limit of normal following operation.

CASE 2.—Mrs. P. M., married, aged 70 years, was seen in June, 1930, complaining of palpitation, "smothering spells" at night, consciousness of the heart's action and nervousness. These symptoms had been present with varying degree for several years. There was increased perspiration. The weight had not varied more than a few pounds. On physical examination the patient was found to be short and stout. There was no exophthalmos, but a suggestive stare was noted; there was no lid-lag. The neck was short and the thyroid was palpated with some difficulty; it was firm and nodular, a typical adenomatous goiter. The heart was enlarged to the left, the apex being in the fifth interspace, 12 cm. from the midline, and slightly heaving. The blood pressure was 200/120 mm.; the pulse rate 96. There was a fine tremor of the fingers. A determination of the basal metabolic rate could not be made at this time. The patient was given Lugol's solution, ten drops, three times a day for two weeks. There was improvement in all the symp-

toms, and the blood pressure decreased to 150/90 mm.; pulse rate 84. In September the patient entered the hospital for operation. The symptoms and physical findings remained as they were at the original examination. The basal metabolic rate was -6 and +1 per cent. The blood pressure was 196/110 mm. A subtotal thyroidectomy was performed, from which the patient made a good recovery. She has been feeling well since then and has been entirely relieved of her symptoms. Her blood pressure following operation was 152/84 mm.

CASE 3.—Mrs. K. H., aged fifty-one years, was seen November 20, 1928. She was emotional, crying easily. She complained of tachycardia, consciousness of the heart's action, a feeling of nervous tension and tremor of the hands. These symptoms had been troublesome for about one year. There was no increase of perspiration and no loss of weight. The patient has had a goiter for many years. Physical examination showed a woman 5 ft. 2½ in. tall, weight 146 lb. The color was good. There was no exophthalmos, lid-lag or stare. The thyroid was enlarged and firm, the left lobe somewhat larger than the right. The consistence was uneven, indicating the presence of adenomata. The heart was normal in size, the sounds loud and clear, the rate 100, rhythm regular. The blood pressure was 136/76 mm. There was a fine tremor of the fingers. The remainder of the physical examination was negative. Differential count showed 58 per cent lymphocytes. Red and white counts and hemoglobin were normal. On November 27 the basal metabolic rate was +1 and +7. Subtotal thyroidectomy was done January 2, 1929. An adenomatous goiter was found. Recovery was uneventful. On March 2, 1929, the patient was re-examined. She felt better in all respects. The nervousness had disappeared. There was no longer throbbing in the arteries, and the hands were steady. The pulse rate was 84, blood pressure 126/74 mm. Basal metabolic rates were +5 and +8 per cent.

CASE 4.—Mrs. C. E. M., aged fifty-nine years, was seen September 9, 1929. For eight years she had had attacks of diarrhea which lasted about one week. She had about six attacks a year. For more than a year she had lost strength and had lost 18 pounds in weight in the last six months. She had been very nervous for several months, and her hands had been unsteady in sewing and writing. There was no history of rheumatic fever. The patient was a small woman, height 5 feet, weight 112 pounds. She looked older than her age. There was no exophthalmos, but a definite stare and lid-lag were noted. There was a marked tremor of the fingers. Both lobes of the thyroid were enlarged and adenomatous. The heart apex was 8.5 cm. to the left in the fifth interspace. Relative dullness measured 2 × 10 cm. Auricular fibrillation was present. The heart rate was 32 to the quarter minute. There was a systolic apical murmur. The pulmonic second sound was not accentuated. The blood pressure was 150/80 mm. for the largest beats. There was no edema. Basal metabolic rates on September 10 were +4 and +7. Subtotal thyroidectomy was performed on September 17, from which the patient made a good recovery. One week following operation, the heart became regular. Subsequently, the tremor and nervousness disappeared and the patient gained 20 pounds. The basal metabolic rate was not determined following operation. Symptomatic recovery has been complete.

COMMENT

These cases illustrate the importance of a careful investigation of the thyroid and, when indicated, the beneficial results which may be obtained through operation. *The basal metabolic rate, while very helpful when it is elevated, is a sign which should be ignored, when normal or*

subnormal, in the presence of unmistakable evidence of thyrotoxic symptoms and signs.

The circulatory manifestations are often more pronounced than in the cases cited. Every case of auricular fibrillation should have careful study of the thyroid; rheumatic heart disease may be associated with thyroid disease. Operation may largely relieve the circulatory symptoms. At times the goiter is substernal, being demonstrable only by x-ray examination.

The explanation of the low basal metabolic rate in the cases under discussion is not clear. The symptoms and signs are those of hyperthyroidism rather than of myxedema. Yet subtotal thyroidectomy either raises the metabolic rate when it is subnormal or, when normal, leaves it practically unchanged. Signs of myxedema with low metabolic rate would undoubtedly follow if too much of the gland were removed, but as yet we have not encountered such instances among our cases. It is noteworthy, too, that both subjective and objective improvement may be obtained with Lingol's solution prior to operation, just as in hyperthyroidism.

An important fact to keep in mind in connection with the thyroid heart is that it is the one type of heart disease which is preventable.

In any patient in whom the pulse pressure and the blood pressure are increased without apparent cause, thyroid disease should be suspected. Usually the systolic pressure is elevated; often both systolic and diastolic pressures are raised.

In all patients with cardiac neuroses, the possibility of disease of the thyroid gland should never be lost sight of. Careful study of the case often reveals a "burned out" hyperthyroidism or an adenomatous thyroid. Subtotal thyroidectomy may result in cure.

In patients with organic heart disease, the thyroid may be a contributing, at times a dominant, factor in the production of symptoms. The frequency with which a thyroid dyscrasia is found, depends upon the care exercised in looking for it.

REFERENCES

1. Levine, Samuel A.: Unrecognized Hyperthyroidism Masked as Heart Disease, *Ann. Int. Med.* 4: 67, 1930.
2. Hamburger, W. W., and Lev, M. W.: Masked Hyperthyroidism, *J. A. M. A.* 94: 2050, 1930.
3. Morris, Roger S.: The "Thyroid Heart" With Low Basal Metabolic Rate, *Am. J. M. Sc.* 181: 297, 1931.

THE STATUS OF THE HEART IN MYXEDEMA*

C. L. TUNG, M.D.

PEIPING, CHINA

THE condition of the cardiovascular system in myxedema is still controversial. Zondek in 1918,¹ Assmann in 1919,² Meissner in 1920,³ and Fahr in 1925⁴ and in 1927,⁵ have described cases in which dilatation of the heart both to the right and to the left and signs of cardiac failure were relieved only by thyroid therapy. Willius and Haines,⁶ studying a large number of cases of myxedema in 1925, found no characteristic cardiovascular changes.

As to the electrocardiographic changes in myxedema, Zondek described cases in which the P- and T-waves were absent, and reappeared after thyroid medication. Fahr found the P-wave present in his cases; he considered a negative T-wave in Leads I and II the most characteristic change. Lueg⁷ and Nobel, Rosenblüth and Samet⁸ state that the increased resistance of the skin may account for the "absence" of P- and T-waves. This explanation is, according to Wilson,⁹ untenable, since the electrical capacity introduced into the circuit by the high resistance of the myxedematous skin should be eliminated by proper preparation of the skin before the electrocardiogram is taken.

Thatcher and White¹⁰ in 1926 published a careful study of the electrocardiograms in 14 cases of myxedema in all of which there was a low T-wave in Lead II. They also noted a general decrease in the amplitude of all electrocardiographic deflections in all leads before treatment, with an increase after treatment with thyroid extract. They concluded that there is a distinct parallelism between the height of the T-wave in the electrocardiogram and the basal metabolic rate in hypothyroidism.

Willius and Haines,⁶ in analyzing the electrocardiograms in 55 cases of myxedema, found the curves, aside from graphic evidence suggestive of ventricular preponderance, to be normal in 28 of them and abnormal in 12. The abnormalities in the latter group consisted chiefly in T-wave negativity, with disappearance of negativity after thyroid medication.

Reid and Kenway¹¹ recently studied the electrocardiograms of 260 patients with various clinical conditions, who had a basal rate between minus 10 per cent and minus 48 per cent, and discovered no electrocardiographic findings characteristic of low basal metabolism. The definitely myxedematous subjects, of which there were 5, all showed low T-waves; 4 showed low P-waves as well.

*From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

With the object of obtaining additional evidence bearing upon the condition of the heart in myxedema, I have gone through the records of all patients diagnosed as having myxedema during the last eight years at the University of Michigan Hospital. Cases diagnosed "hypothyroidism" were not included in this study, since this diagnosis was usually based on a slightly lowered basal rate, often not lower than minus 20 per cent, and since no roentgenologic or electrocardiographic examinations were made in these cases. There were 18 cases, diagnosed as myxedema, in which electrocardiograms were available. In all of these patients the basal metabolic rate was minus 25 per cent or lower, with the exception of one who had received a few doses of desiccated thyroid before the first determination. In this case the basal rate was minus 18 per cent. There were only 7 cases in which electrocardiograms were made both before and after treatment.

Of the 18 subjects studied, 13 were women and 5 men. The average age was forty-seven years; 4 patients were under thirty-nine years, 5 between forty and forty-nine years, and 9 over fifty years of age. All of them presented the typical signs and symptoms of myxedema. In practically all of the cases the heart sounds were described as faint; in some instances they were almost inaudible. Seven patients presented symptoms and signs of first degree cardiac insufficiency; in 5 of these the heart was enlarged; in the other two it appeared to be normal in size. These patients complained of dyspnea on exertion and showed pitting edema over the ankles and feet.* Eleven patients had no cardiac failure. Fluoroscopic and teleroentgenographic examinations of the heart were carried out in 15 cases. In the reports of the fluoroscopic examination the heart is often described as showing indistinct or feeble pulsation of its borders. The heart was enlarged, either on roentgen ray or on physical examination, in 9 patients; 5 of these showed an aortic or hypertensive type of enlargement with a prominent aortic knob. In all of these cases either hypertension or general arteriosclerosis was present. It was considered not enlarged in 9 cases, 3 of which showed a rather prominent aortic knob in the remainder the heart was apparently normal in shape. Seven of the entire group showed peripheral and retinal arteriosclerosis; 8 had no evident arteriosclerosis; in 3 patients, the condition of the peripheral and retinal vessels was not mentioned. Of the group of 7 who showed general arteriosclerosis, 2 were between forty-five and forty-nine years, and 5 over fifty years of age. The presence of arteriosclerosis

*Erythrocyte counts and hemoglobin determinations were made in 17 cases. The average red cell count was 3.8 million per c. mm., and the average hemoglobin value (Sahli) was 73 per cent. Of the seven patients who showed pitting edema of the lower extremities, all had hemoglobin readings above 68 per cent and red blood cell counts above 3.8 million, per c. mm., except one with 3.5 million. It is not probable that the pitting edema of the lower extremities observed in these patients was due to the anemia. Four patients in which the red counts and hemoglobin readings were below 3.5 million and 68 per cent respectively, did not show pitting edema.

may have been related more to the process of senility than to the duration of myxedema, since of the 6 cases with myxedema of ten or more years' duration, only 2 showed moderate peripheral arteriosclerosis, and 4 showed none. Seven patients showed a systolic blood pressure exceeding 150 mm. Hg., or a diastolic pressure in excess of 90 mm. Hg. or both. In the others there was no evidence of hypertension. Only one of the 6 patients who had suffered from myxedema for ten years or more had hypertension. Apparently, the blood pressure is often low in patients with myxedema of long duration. Excluding the one case in which the first basal rate was made after several doses of thyroid extract had been given, the average basal metabolic rate of the 17 subjects was minus 33 per cent.

ELECTROCARDIOGRAPHIC FINDINGS

The average heart rate, determined from the initial electrocardiograms made before treatment was begun, was 71 per minute, while the average rate taken during the first basal metabolic rate determinations was 9 beats less, or 62 per minute. The P-R interval was essentially normal, except that it was slightly prolonged in 3 subjects; in two of these it measured 0.2 second and in one 0.22 second. The duration of the initial ventricular deflection, QRS, varied between 0.06 and 0.08 second, and was, therefore, normal in all cases. The minimum, average, and maximum amplitudes in millimeters of the deflections P, R, S, and T are given in Table I. Compared with simi-

TABLE I

AMPLITUDE IN MILLIMETERS OF DEFLECTIONS IN EIGHTEEN CASES OF MYXEDEMA

| | LEADS | P | R | S | T |
|---------|-------|------|------|------|------|
| Minimum | I | 0. | 1.2 | 0.4 | -2.0 |
| Mean | | 0.4 | 5.5 | 0.5 | -0.1 |
| Maximum | | 1.0 | 10.0 | 2.0 | 1.6 |
| Minimum | II | 0. | 0. | 0. | -1.5 |
| Mean | | 0.6 | 5.1 | 0.5 | -0.3 |
| Maximum | | 1.4 | 11.0 | 4.0 | 1.0 |
| Minimum | III | -1.0 | 0. | 0. | -1.2 |
| Mean | | 0.2 | 1.6 | 2.0 | -0.2 |
| Maximum | | 0.5 | 6.0 | 10.0 | 1.0 |

Note: Each millimeter = 10^{-4} volt. One patient showed auricular fibrillation.

larly tabulated values obtained in 52 normal students by Lewis,¹² the mean values of the P-deflections in Leads II and III are only one-half and one-fourth, respectively, of the mean figures for the same leads of Lewis' normals. The mean amplitudes of the R-waves in Leads II and III are likewise only one-half and one-fourth the normal values. The difference in the amplitudes of these deflections is too great to be entirely accounted for by the difference in the average age between this group and that of normal students studied by Lewis.

Still more definite and conspicuous are the changes in the T-deflections. The minimum, average, and maximum values of the T-waves in the myxedema cases are far below the normals of Lewis. The average amplitude of the T-deflection in Lewis' normal subjects was: Lead I, 1.93 mm.; Lead II, 2.46 mm.; and Lead III, 0.61 mm.; while the corresponding averages in myxedema are: minus 0.1, minus 0.3, and minus 0.2 mm. respectively. In fact, the maximum height of this deflection in Leads I and II of my series is definitely less than the

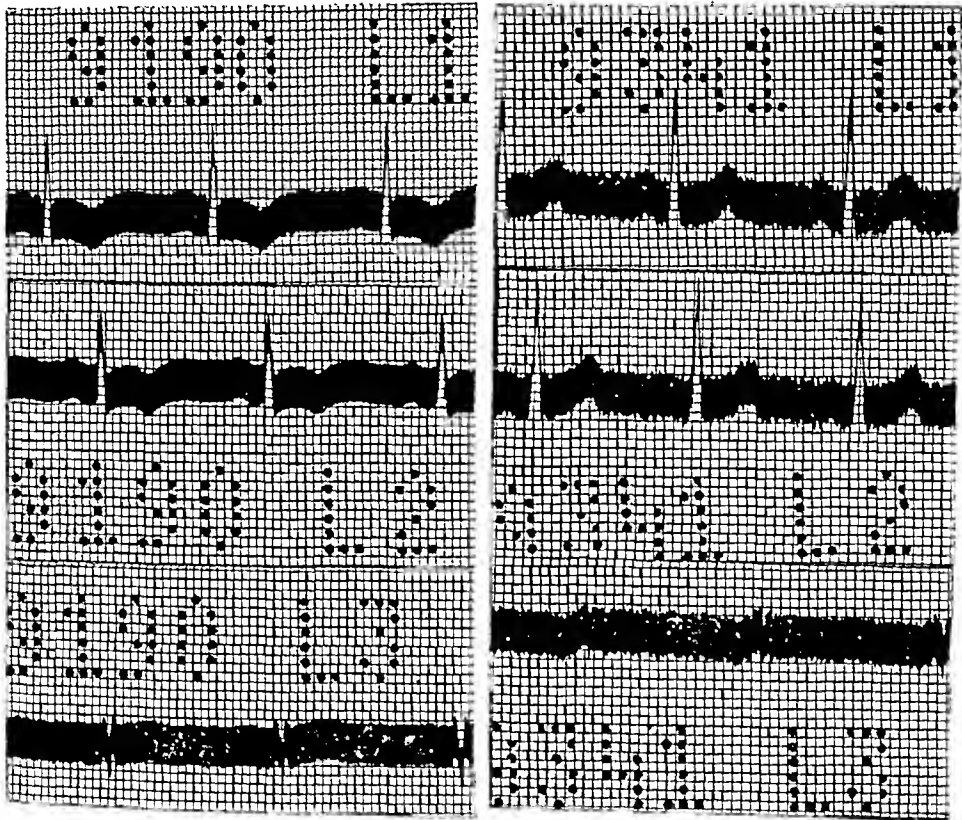


Fig. 1.—(Case 3.) E.k.g. No. 9190, taken September 29, 1927, before thyroid therapy, when basal metabolic rate was minus 36 per cent. E.k.g. No. 9341, taken October 22, 1927, after thyroid therapy when basal metabolic rate was plus 8 per cent.

average height in the corresponding leads of Lewis' series. Table II gives the direction of the T- and P-deflections of the 18 cases before treatment. Inversion of T in Lead I, or in Leads I and II occurred in 6 patients; inversion of T in Leads II and III occurred in 6 cases; inversion of T in all leads occurred once; and flat T-waves in all three

TABLE II

DIRECTION OF T- AND P-WAVES IN EIGHTEEN CASES OF MYXEDEMA

| LEAD | T-WAVES | | | P-WAVES | | | |
|------|----------|------|---------|----------|------|---------|----------|
| | INVERTED | FLAT | UPRIGHT | INVERTED | FLAT | UPRIGHT | DIPHASIC |
| I | 6 | 5 | 7 | 0 | 1 | 16 | 0 |
| II | 10 | 5 | 3 | 0 | 1 | 16 | 0 |
| III | 8 | 6 | 4 | 3 | 8 | 5 | 1 |

leads occurred twice. The T-deflections were, therefore, definitely abnormal in 15 out of 18 patients. When upright, they were not more than 1.6 mm. in height in Lead I, and not more than 1.0 mm. in the other two leads.

In only 7 patients of this series was an electrocardiogram taken after the basal rate was brought back to an approximately normal level by thyroid medication. As changes in the electrocardiograms following treatment constitute definite evidence that the deviations from normal found in the curves before treatment are attributable to myxedema, the data in each of these 7 subjects are tabulated in detail in Table III. It will be noticed that although the P- and QRS-deflections tended to

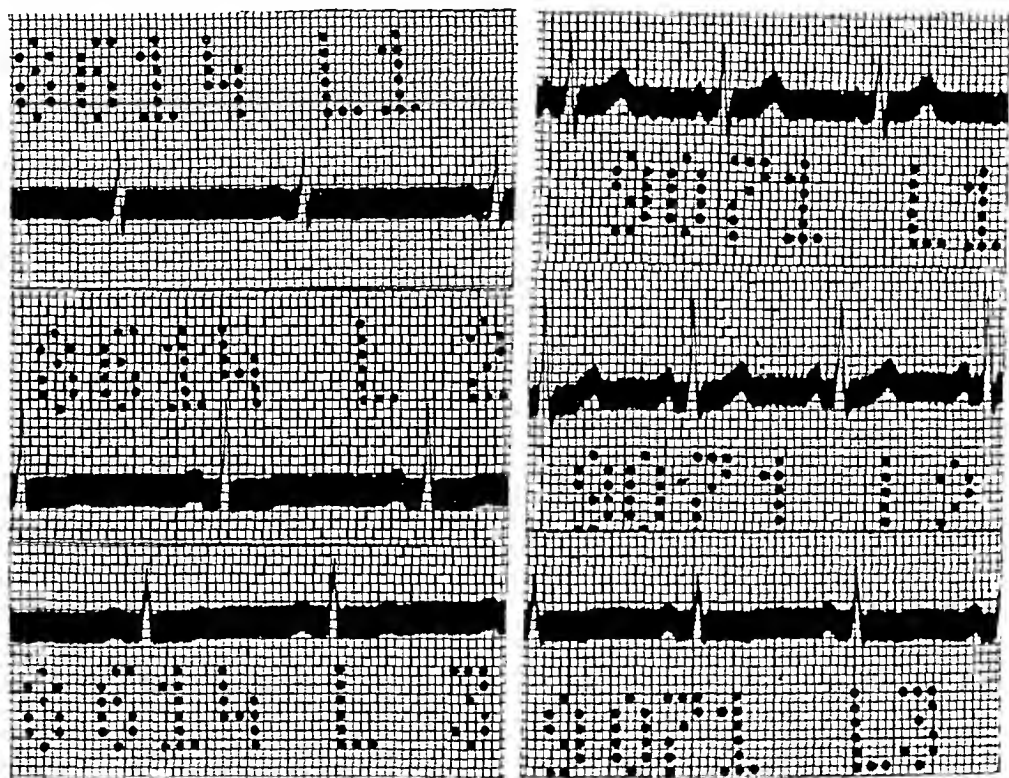


Fig. 2.—(Case 2.) E.k.g. No. 8614, taken June 21, 1927, before thyroid therapy, when basal metabolic rate was minus 27 per cent. E.k.g. No. 9071, taken September 8, 1927, after thyroid therapy, when basal metabolic rate was plus 2 per cent.

rise following treatment, the chief alteration consisted in the direction and amplitude of the T-deflections in Leads I and II, where all inverted or flat T-deflections became definitely upright, and low T-waves assumed a greater amplitude. There is, however, a tendency in all but one case for the T-wave in the third lead to become or remain flattened or inverted following treatment. Figs. 1, 2, and 3 illustrate the changes in the electrocardiograms of three of these patients produced by treatment.

In only one patient (Case 4) were teleroentgenograms taken both before and after thyroid treatment. This patient presented slight

cardiac insufficiency, with a transverse cardiac diameter of 15 cm. before taking desiccated thyroid. When the basal rate was brought up to minus 9 per cent, the transverse cardiac diameter was 12.75 cm. In the other cases, no follow-up x-ray examination of the heart was made.

It would not be profitable here to speculate upon the significance of the inversion of the final ventricular deflection. Whether it is due to myocardial anoxemia, consequent upon diminished blood flow through the coronary vessels, to a myxedematous change in the heart muscle,

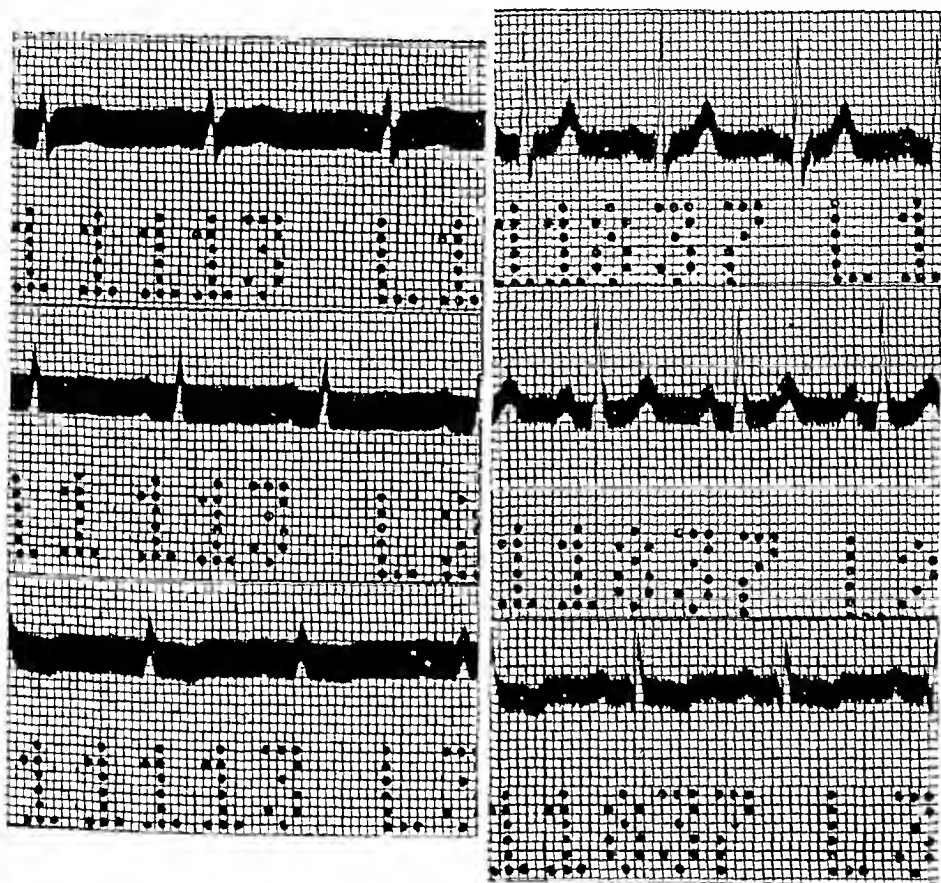


Fig. 3.—(Case 4.) E.k.g. No. 11113, taken November 23, 1928, before thyroid therapy, when basal metabolic rate was minus 31 per cent. E.k.g. No. 11837, taken May 9, 1929, after thyroid therapy when basal metabolic rate was minus 9 per cent.

or to some other cause, is at present uncertain. Whatever the actual mechanism underlying the T-wave inversion, it is probably dependent upon a functional change in the gradient of the ventricular musculature, involving a change in the duration of systole in the various parts of the ventricles. It is interesting to note again that all inverted or flat T-deflections became definitely upright after the basal metabolic rate was brought back to an approximately normal level, indicating that the cardiac damage is not necessarily permanent.

In the seven cases, which presented signs of cardiac insufficiency before treatment, all such signs disappeared after thyroid therapy.

TABLE III
ELECTROCARDIOGRAPHIC DATA OF SEVEN MYXEDEMA PATIENTS BEFORE AND AFTER THYROID TREATMENT

| NO. | SEX | AGE | DATE | ELECTROCARDIOGRAM AMPLITUDE IN MILLIMETERS EACH MM. = 10-1 VOLT | | | | | | | RATE | P-R (SEC.) | QRS | T | P | LEAD | HEART AND PERIPHERAL BLOOD VESSELS | RAIR % |
|-----|-----|-----|--------------------------------------|--|------|------|------|-------|------|-------|------|---------------|-------|------|------|------|--|-----------|
| | | | | I | II | III | I | II | III | I | II | III | I | II | III | | | |
| 1. | M | 58 | Jan. 3, 1927 (Before treatment) | +0.4 | +0.2 | -0.2 | -0.2 | +8.0 | +5.0 | +5.0 | 56 | 0.18 | +8.0 | -0.2 | +0.4 | I | Heart enlarged, and hypertensive in type. Aortic arch prominent. Slight general arteriosclerosis. | -28 |
| | | | | +0.2 | -0.2 | flat | flat | +5.0 | -3.0 | +8.0 | | | +5.0 | -0.2 | +0.2 | II | | |
| | | | | -0.2 | +0.4 | +2.0 | +1.0 | +8.0 | +7.0 | -2.8 | 54 | 0.18 | +8.0 | flat | +0.6 | I | | |
| | | | | flat | flat | -1.2 | flat | -2.8 | +7.0 | +5.0 | | | -2.8 | +1.0 | flat | III | | |
| 2. | F | 44 | June 21, 1927 (Before treatment) | +0.2 | +0.8 | flat | flat | +5.0 | +8.0 | +2.0 | 60 | 0.17 | +5.0 | flat | +0.2 | I | Heart normal in size and shape. Aortic arch not prominent. No general arteriosclerosis. | -27 |
| | | | | +0.8 | +0.5 | +0.4 | +0.6 | +8.0 | +3.5 | +5.0 | | | +8.0 | flat | +0.5 | II | | |
| | | | | +0.5 | +0.6 | +2.0 | +1.8 | +5.0 | +8.0 | +3.5 | 80 | 0.15 | +5.0 | +0.4 | +1.0 | I | | |
| | | | | +1.6 | +1.0 | -0.2 | -0.2 | +8.0 | +3.5 | +7.0 | | | +8.0 | -0.2 | +0.4 | II | | |
| 3. | F | 51 | Sept. 29, 1927 (Before treatment) | +0.2 | +0.5 | -2.0 | -1.5 | +7.0 | +6.0 | +2.0 | 70 | 0.16 | +7.0 | -2.0 | +0.2 | I | Heart slightly enlarged and of hypertensive type. Aortic arch normal. No mention of peripheral arteries. | -36 |
| | | | | +0.5 | flat | +0.6 | +0.6 | +6.0 | -2.0 | +10.0 | | | +6.0 | -1.5 | +1.0 | II | | |
| | | | | flat | +1.0 | +1.8 | +1.8 | +10.0 | +9.0 | +9.0 | 80 | 0.15 | +10.0 | +1.8 | +0.4 | I | | |
| | | | | +1.0 | +0.4 | +1.8 | +1.8 | +9.0 | +9.0 | -1.0 | | | +9.0 | +1.8 | -0.8 | II | | |

TABLE III—CONT'D

| ELECTROCARDIOGRAM AMPLITUDE IN MILLIMETERS EACH MM. = 10 ⁻⁴ VOLT | | | | | | | | | | BMR % | VESSELS |
|--|-----|-----|-------------------------------------|------|------|------|---------------|---------------|------|----------|---|
| NO. | SEX | AGE | DATE | LEAD | P | T | QRS | P-R (SEC.) | RATE | | |
| 4. | F | 51 | Nov. 23, 1928 (Before treatment) | I | +0.2 | +0.4 | +3.5 -2.0 | 0.18 | 75 | -31 | Heart markedly enlarged, especially the left ventricle. Aortic arch slightly prominent. Transverse diameter, 15 cm. No general arteriosclerosis. Definite diminution in size of cardiac shadow in teleroentgenogram. Present transverse diameter, 12.75 cm. Aortic arch still prominent. |
| | | | | II | +0.6 | -0.2 | +4.0 | | | | |
| | | | | III | +0.2 | -0.8 | +2.5 | | | | |
| | | | May 9, 1929 (After treatment) | I | +0.8 | +3.2 | +11.0 -2.0 | 0.16 | 96 | -9 | Heart not enlarged. No x-ray examination. No peripheral arteriosclerosis. |
| | | | | II | +1.4 | +2.0 | +11.0 | | | | |
| | | | | III | +1.2 | -1.0 | +4.0 | | | | |
| 5. | F | 24 | Dec. 19, 1930 (Before treatment) | I | +1.0 | +0.6 | +10.0 | 0.15 | 72 | -34 | Heart normal in size and shape. Aorta not mentioned. Marked peripheral arteriosclerosis. |
| | | | | II | +1.4 | +0.8 | +11.0 | | | | |
| | | | | III | +0.4 | flat | +1.2 | | | | |
| | | | Mar. 26, 1931 (After treatment) | I | +1.0 | +2.2 | +8.0 | 0.15 | 68 | -11 | |
| | | | | II | +1.4 | +3.0 | +12.5 | | | | |
| | | | | III | +0.4 | +1.0 | +4.5 | | | | |
| 6. | F | 65 | Jan. 29, 1931 (Before treatment) | I | +0.6 | +0.4 | +4.0 -0.4 | 0.20 | 75 | -28 | |
| | | | | II | +0.8 | flat | +1.4 | | | | |
| | | | | III | flat | -0.6 | -2.5 | | | | |
| | | | Mar. 20, 1931 (After treatment) | I | +1.0 | +1.8 | +7.0 | 0.18 | 100 | -4 | Heart slightly enlarged, more toward left, than right. Aortic arch slightly widened. No peripheral arteriosclerosis. |
| | | | | II | +1.8 | +1.2 | +2.0 | | | | |
| | | | | III | +0.6 | -1.0 | -5.0 | | | | |
| 7. | M | 49 | Mar. 6, 1931 (Before treatment) | I | +1.0 | -0.4 | +5.0 | 0.20 | 90 | -47 | |
| | | | | II | +1.0 | -1.0 | +6.0 | | | | |
| | | | | III | flat | -0.4 | +1.8 | | | | |
| | | | Apr. 23, 1931 (After treatment) | I | +1.0 | +0.6 | +9.0 | 0.18 | 95 | -16 | |
| | | | | II | +1.2 | +0.6 | +9.0 | | | | |
| | | | | III | +0.8 | flat | +1.0 | | | | |

The definite response of these patients to substitution therapy and their failure to respond to digitalis are evidence that the clinical syndrome which has been referred to as a "myxedema heart" does exist in a certain proportion of patients with high grade myxedema and is due to a lack of sufficient thyroid secretion. Although cardiac insufficiency occurred in only a little more than one-third of these patients, the electrocardiogram demonstrated cardiac abnormalities in more than three-fourths of them. Perhaps, only a small number develop definite signs of cardiac weakness because of the diminished metabolism and activity which characterize the disease.

SUMMARY

This study is based upon an analysis of the hospital records of eighteen cases of definite myxedema with an average basal metabolic rate on admission of minus 33 per cent. The average age of these patients was forty-seven years. Seven of these patients showed evidence of cardiac insufficiency; nine had enlargement of the heart; seven had hypertension; and in seven a definite generalized arteriosclerosis was noted. There did not appear to be any definite relation between the presence of hypertension or arteriosclerosis and the duration of the myxedematous state. The symptoms and signs of cardiac weakness disappeared under thyroid medication. In all cases, the electrocardiogram showed P-waves and QRS-waves of relatively small amplitude. The most striking abnormality was the flattening or inversion of the T-deflection which disappeared after treatment in the seven cases in which the electrocardiographic examination was repeated after the basal metabolic rate had returned to normal.

The writer wishes to acknowledge his indebtedness to Dr. Frank N. Wilson for his encouragement and valuable suggestions.

REFERENCES

1. Zondek, H.: *München. med. Wchnschr.* 65: 1180, 1918; 66: 681, 1919.
2. Assmann, H.: *München. med. Wchnschr.* 66: 9, 1919.
3. Meissner, R.: *München. med. Wchnschr.* 67: 1316, 1920.
4. Fahr, G.: *J. A. M. A.* 84: 345, 1925.
5. Fahr, G.: *AM. HEART J.* 3: 14, 1927.
6. Willius, F., and Haines, S.: *AM. HEART J.* 1: 67, 1925.
7. Lueg, W.: *Ztschr. f. klin. Med.* 104: 337, 1926.
8. Nobel, E.: Rosenblüth, A., and Samet, B.: *Ztschr. f. exper. Med.* 43: 332, 1924.
9. Wilson, F. N.: Personal communication to the author, 1931.
10. Thacher, C., and White, P. D.: *Am. J. M. Sc.* 171: 61, 1926.
11. Reid, W. D., and Kenway, F. L.: *Endocrinology* 13: 191, 1929.
12. Lewis, T.: *Clinical Electrocardiography*, Ed. 3, 22, 1923, Shaw and Sons, London.

THE MECHANISM OF DEATH OF THE HUMAN HEART AS RECORDED IN THE ELECTROCARDIOGRAM*

KENNETH B. TURNER, M.D.
NEW YORK, N. Y.

THE mode of death of the human heart, while it has claimed the attention of clinicians from time to time, has been mainly of academic interest. The demonstration in recent years that certain measures designed to revive a dying myocardium may at times be successfully employed makes desirable an analysis of existing knowledge of the sequence of events which immediately precedes the cessation of cardiac activity. Hearts which have apparently ceased to beat have resumed contraction following the intracardiac injection of adrenalin, after manual massage, or from the mechanical irritation caused by needle puncture alone as pointed out by Hyman.¹ The therapeutic use of oxygen has served to support a severely damaged heart muscle during periods of profound weakness until functional recovery has made possible resumption of a circulation adequate for the continuation of life.

It is the purpose of this paper to analyze the cases previously recorded, to supplement these with five additional reports, and to determine any possible therapeutic application of our existing knowledge of the dying human heart.

REVIEW OF THE LITERATURE

The first reference to electrocardiographic studies of the dying human heart is by Rohmer² who reported before the Section of Pediatrics of the *Deutscher Naturforscher und Aerzte* his observations in three fatal cases of diphtheria. He believed that the records showed complete dissociation of auricles and ventricles and noted further that the form of the QRS group was abnormal. So far as can be determined, these observations were never published as a paper.

In 1912 Robinson³ made records of seven patients who died of acute infections (two of poliomyelitis, one of pneumococcus meningitis, four of pneumonia). Cardiac activity persisted for from six to thirty-five minutes after clinical death had occurred. In four cases, ventricular activity outlasted the auricular, while in two, the auricles continued to beat after the ventricles had stopped. Both auricles and ventricles ceased simultaneously in the remaining case. "Marked slowing of the rate of cardiac activity always occurred and there was usually distinct delay in the conduction time between auricles and ventricles. Com-

*From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital.

plete dissociation was seen in three cases. Ventricular fibrillation occurred in two cases, in one of which the ventricles again established a regular rhythm. Evidence of auricular fibrillation was never seen. Characteristic changes in the ventricular electrical complex occurred in all these cases. They consisted of a decrease in the size of the R-wave and an increase in the size of the T-wave, and a tendency to a fusion of these waves. There was usually but little change in the duration of the ventricular complexes as the cardiac activity gradually ceased." From these observations, Robinson concluded that "when death occurs from an acute infectious disease, there is no one point in the human heart which may be considered as the 'ultimum moriens.'"

Electrocardiographic records were made by Halsey⁴ during the death of a patient from bronchopneumonia. The heart rate slowed markedly, with a gradual prolongation of auriculoventricular conduction and a change in the form of QRS. An idioventricular rhythm appeared and auricular activity ceased. Ventricular fibrillation appeared shortly before the death of the heart.

The first records reported of patients dying of intrinsic cardiac disease were those of Dieuaide and Davidson.⁵ In two cases electrocardiograms were taken during the death of the heart, while in a third case, the last record was taken three hours before death. The first two patients could probably be classified as cases of arteriosclerotic-hypertensive heart disease. The third case was one of rheumatic heart disease. Certain features were common to all three cases from an electrocardiographic standpoint, namely, a gradual slowing of cardiac rate, together with lengthening of P-R, QRS, and Q-T intervals; diminution of the amplitude of R and T; and A-V nodal rhythm or complete dissociation of auricles and ventricles. Various arrhythmias were observed, including auricular and ventricular extrasystoles, ventricular tachycardia, and auricular and ventricular fibrillation. Transient ventricular fibrillation occurred in the first case after all evidence of auricular activity had disappeared. Death occurred following a series of abnormal complexes, presumably of ventricular origin, which gradually slowed in rate and decreased in amplitude. In the second case, complete dissociation of auricles and ventricles also occurred. There was transient auricular fibrillation and there were brief runs of ventricular tachycardia. In the third case, transient ventricular tachycardia was observed three hours before death.

In an excellent study based on observations in twenty cases, Schellong⁶ noted the frequency of A-V nodal rhythm, and found that this was often interrupted by beats of sinus origin. He believed that a lengthening of the P-R interval always went parallel with a decrease in rate during the first stage of death of the heart and that these changes were due to vagus activity. Complete auriculoventricular dissociation was found to occur in dying hearts, not as the result of a conduction

disturbance, but whenever the sino-auricular frequency fell below that of the A-V node. However, partial heart-block was not uncommon. Two cases showing auricular fibrillation died with gradual slowing of the circus movement. Schellong stated that the appearance of ventricular fibrillation depended upon the ability of the heart muscle to form ectopic impulses of sufficient frequency, regardless of the presence or absence of auricular fibrillation. In the two cases of ventricular fibrillation observed by him, both developed after a ventricular tachycardia. The T-waves in the dying hearts were noted to increase in size and to become positive even when previously negative.

Willius⁷ reported four cases in detail and referred to two others in his series in which he found that, as death approached, auricular activity always ceased before that of the ventricles. Auricular fibrillation was present twice at the beginning of electrocardiographic study, but did not occur as an intercurrent event. Transient auricular flutter occurred once. A-V nodal rhythm was present in five cases. Complete heart-block was found three times, sino-auricular standstill twice, prolonged conduction and partial heart-block each once. Periods of cardiac standstill occurred in three cases, lasting 9.4 seconds in each of two patients, and 11.4 seconds in the third. Ventricular fibrillation occurred in four cases, and was terminal in three. A tendency to fusion of R and T was found in three cases. The four patients reported fully consisted of two cases of hyperthyroidism, one of rheumatic heart disease, and one of rheumatic heart disease with concurrent bacterial endocarditis.

In a study of ventricular tachycardia complicating digitalis therapy, Reid⁸ recorded a change from ventricular tachycardia to a terminal ventricular fibrillation in one case.

Kahn and Goldstein⁹ made observations on seven cases in all of which the sinus node failed first as shown by the establishment of A-V nodal rhythm. Intraventricular conduction defects were common. Ventricular fibrillation was present in two of their cases, once as a terminal event. In their summary, these authors stated that "the cessation of the normal auricular contraction stimulus seems to be the critical phenomenon in the process of death. Before this happens, the sinus node shows irritability and depression in various sequences and degrees and it is probable that if the disturbance could be controlled before cessation of sinus function, recovery might occur. After this happens, it is known experimentally that the heart will not recover although reoxygenated."

In seventeen cases reported by Martini and Sekell¹⁰ the first change was a decrease in rate in most instances. Fatigue of the S-A node led to an A-V nodal rhythm. A new "X" wave frequently appeared between S and T. There was no constant form of the T-wave, but there was a tendency for the R and T waves to merge. In these cases the electrical manifestations did not persist long after clinical death, nine

minutes and thirty-eight seconds being the longest interval recorded. The authors concluded that no constant "ultimum moriens" could be found but that most often it was probably the A-V node.

Willius¹¹ recently summarized the data on this subject and stated "the fairly uniform onset of nodal rhythm, with marked slowing of the heart, and the varied phases of block that frequently are associated with these characteristics, are suggestive of marked vagal action. These phenomena are present at about the time that death appears to have occurred and when, undoubtedly, a marked degree of both cardiac and cerebral asphyxia is present. Cerebral or cardiac asphyxia, or both, have been produced experimentally and graphic transitions have appeared which are similar to those that have been produced by the dying human heart. The later changes observed, namely, long periods of com-

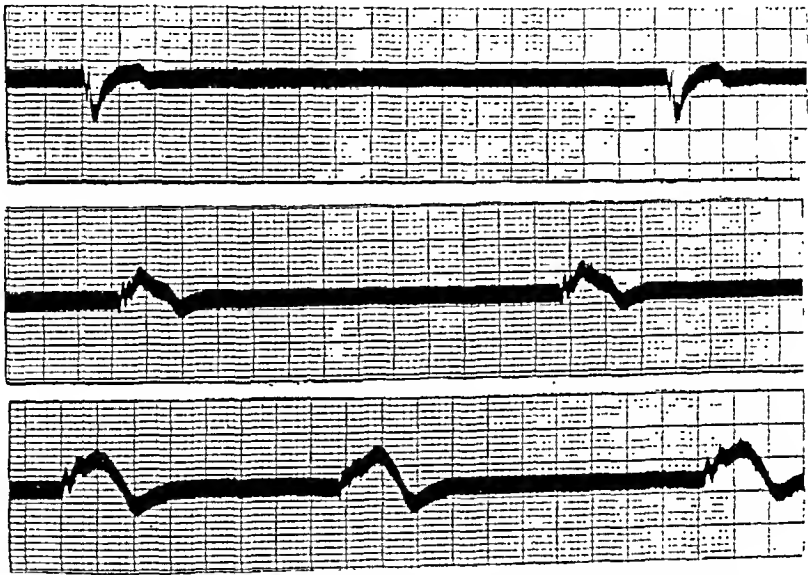


Fig. 1.—Case 1. Leads I, II, and III. About six minutes before clinical death. For full description of this and subsequent figures see text.

plete cardiac asystole, the fusion of component waves, and ventricular fibrillation may result from more profound changes which occur in the musculature itself." Also, in dying, "there is little difference between the records from patients with normal hearts and those from patients with advanced heart disease."

At a recent meeting of the Berliner Medizinische Gesellschaft, Professor v. Hoesslin¹² stated that he had observed electrical activity in hearts for a half-hour or more after clinical death. Ventricular fibrillation was rarely of long duration. Attempts to bring about a restoration of cardiac activity once standstill had occurred were more likely to succeed when the heart was not severely diseased.

CASE REPORTS

CASE 1.—M. S., a 55-year-old unmarried Irish woman, was admitted to the hospital because of gangrene of the left great toe. She was found to have general

arteriosclerosis and a somewhat enlarged heart with a tortuous aorta by x-ray examination. The past history was unimportant. The blood pressure was 112/72 mm. Amputation through the knee was performed, and on the fifth day after operation she complained of difficulty in breathing and pain over the precordium. She rapidly became dyspneic, cyanotic, and pulseless. The electrocardiograms were taken during clinical death, which was believed to have been due to pulmonary embolism. Necropsy was not performed.

Discussion of the Electrocardiograms.—The first electrocardiogram was taken about fifty minutes after the onset of symptoms and six minutes before clinical death (Fig. 1). The record shows bizarre complexes, presumably of ventricular origin, occurring somewhat irregularly

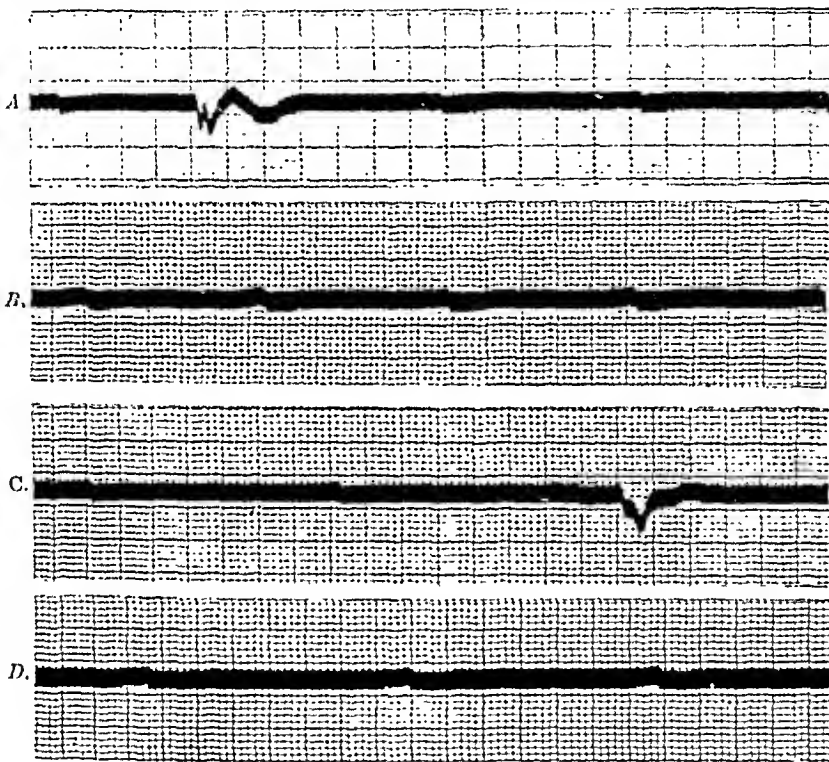


Fig. 2.—Case 1, *A* and *B*. Leads I and II. Taken during clinical death. *C* and *D*. Leads I and II. A few seconds after the preceding.

and at a rate of about 26 per minute. The rate is a little more rapid in Lead III than in Lead I of this record. The main deflection is downward in Lead I and upward in Lead III. In the third lead occur very slight deviations from the base line that may be due to auricular activity.

A second record was taken about two minutes after the first (Fig. 2 *A* and *B*), during the occurrence of clinical death. Throughout this record auricular contractions alone are present with the exception of a single bizarre ventricular complex in the early part. The P-waves, which are upright, occur regularly at a rate of 60 per minute.

The third record was practically continuous with the second. The auricles continue to beat for five minutes after clinical death. The rhythm has become increasingly regular and the rate shows gradual

slowing. Again in this record, a single bizarre ventricular complex occurs. This is the last evidence of ventricular activity. The auricles outlast the ventricles by about fifteen or twenty seconds (Fig. 2 C and D).

CASE 2.—C. T. was a 52-year-old Jewish salesman who was admitted to the hospital in uremia. He was found to have a blood pressure of 185/110 mm., general arteriosclerosis, and a large heart. There was no evidence of cardiac insufficiency. The blood showed a profound secondary anemia, evidence of marked nitrogen retention and acidosis. A loud precordial friction rub was heard. His course was progressively downhill. On the fourth day in the hospital he developed auricular fibrillation. There was a terminal bronchopneumonia. On the morning of the tenth day he had two convulsions and shortly thereafter died. Autopsy showed a chronic glomerulonephritis with general arteriosclerosis, cardiac hypertrophy, acute fibrinous pericarditis, and lobular pneumonia.

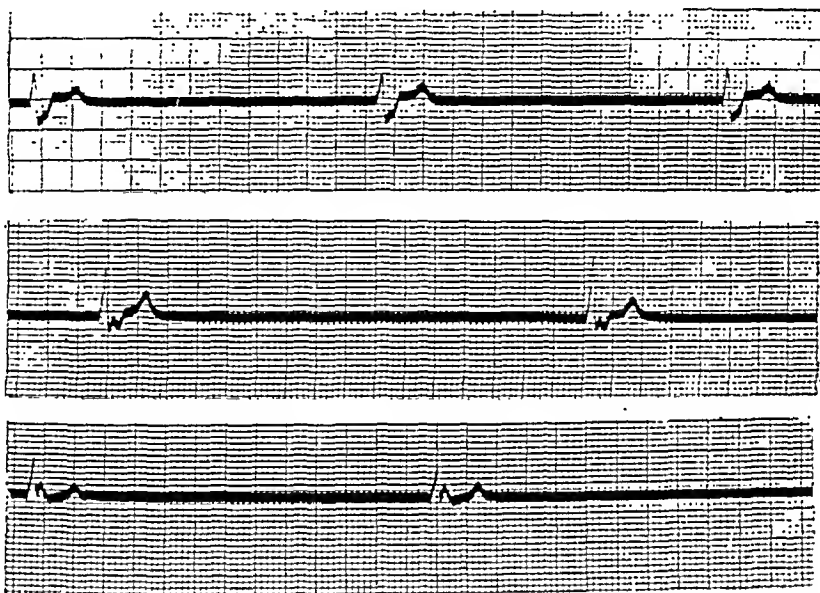


Fig. 3.—Case 2. Leads I, II, and III. About two minutes before clinical death.

Discussion of the Electrocardiograms.—The first electrocardiogram was taken on the fourth day, shortly before the auricles began to fibrillate. The record shows sinus rhythm with a rate of 94. The P-waves are all upright and there is some notching of P₂. The P-R interval is 0.17. S₃ is notched. The T-waves are upright, and those in Leads I and II are unusually prominent. There is an elevation of the S-T interval in all leads but this is not very marked.

The second electrocardiogram was taken six days later during the death of the patient. The record was started at 10:20 A.M. and was practically continuous until 10:24 A.M. when the last evidence of electrical activity was seen. Clinical death of the patient took place at 10:22 A.M., two minutes before the death of the heart. The record begins with a series of regular beats at a rate of 36. Apparently these beats originate in the lower portion of the A-V node with retrograde con-

duction to the auricles, as shown by inversion of P-waves following the QRS complexes (Fig. 3). This rhythm is occasionally interrupted by ectopic ventricular beats without compensatory pause. These beats sometimes replace the beats of nodal origin without disturbance of the rhythm (Fig. 4, *A* and *B*). At one place complete cardiac standstill occurs, lasting 7.2 seconds, followed by a ventricular contraction of the type seen previously, whereupon nodal rhythm is resumed for the space of four beats. Following this series, a succession of four ventricular complexes appears. There is again a period of cardiac standstill, lasting 13 seconds, interrupted once more by a contraction of

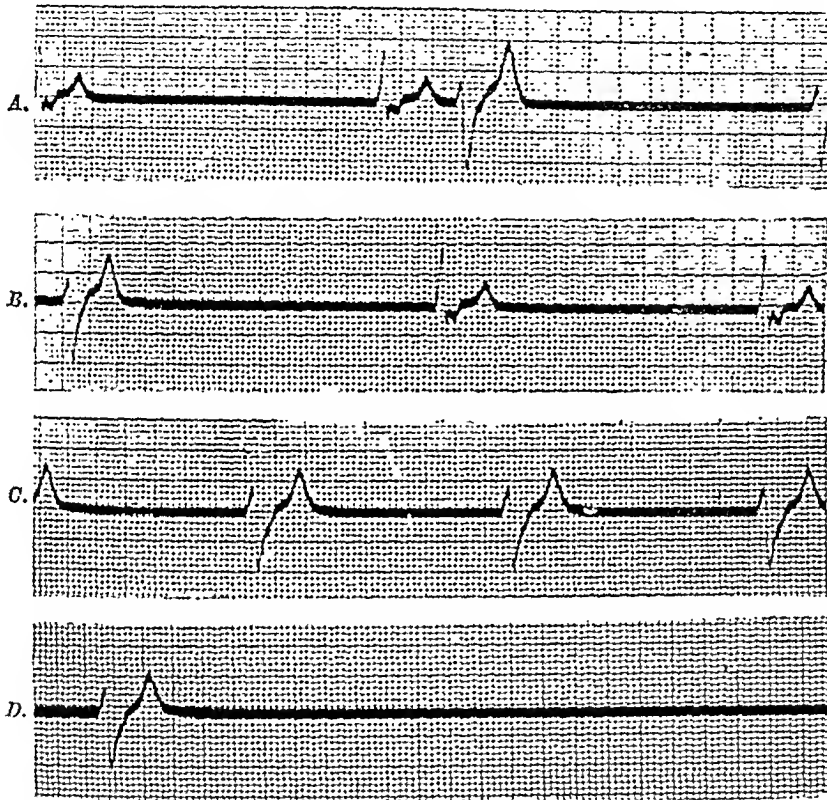


Fig. 4.—Case 2. Lead II. *A* and *B*, About two minutes before clinical death. *C*, Ventricular rhythm preceding cardiac death. *D*, Last evidence of cardiac activity.

ventricular origin. Three more nodal beats appear, of usual form, followed by a succession of ventricular complexes with an irregular rhythm marking the end of cardiac activity. There is no change in form in these terminal complexes, nor is there any diminution in their amplitude (Fig. 4, *C* and *D*).

CASE 3.—J. S. was a 55-year-old contractor who entered the hospital in a comatose state and was found to have syphilitic aortitis with a superimposed subacute bacterial endocarditis. His blood Wassermann reaction was four plus in both antigens and repeated blood cultures showed non-hemolytic streptococci constantly present. An electrocardiogram was taken on the third day in the hospital. On the twelfth day, after gradual improvement in the clinical condition, the patient had several attacks of unconsciousness during which his pulse rate was 34

and regular. Following one of these attacks he died. An electrocardiogram was taken a few minutes before, but not actually during, the clinical death of the patient. An autopsy was not permitted.

Discussion of the Electrocardiograms.—The first record was taken on the third day in the hospital and shows a sinus rhythm with prolonged A-V conduction. The P-R interval is 0.24 sec. The P-waves are upright in the first two leads and partly inverted in Lead III. The ventricular rate is 96. The QRS complexes are somewhat wider than normal measuring 0.13 sec., but this may be partly discounted by the fact that the patient had a very high skin resistance. R_1 and R_2 are notched. T_1 is inverted, while T_2 and T_3 are upright. There is a slight reciprocal displacement of the S-T interval in the first and third

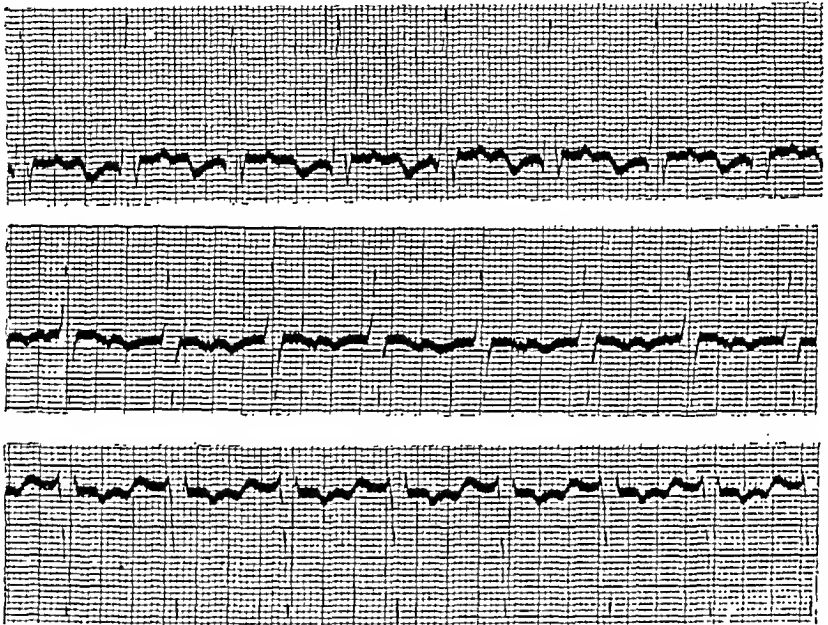


Fig. 5.—Case 3. Leads I, II, and III. Nine days before death.

leads. As the patient was not receiving digitalis, it was thought that the record was definitely indicative of myocardial damage (Fig. 5).

The second record, taken just before clinical death of the patient, begins with a series of P-waves, irregularly spaced, and without any ventricular response. These are succeeded by a short run of bizarre ventricular complexes, varying in form and amplitude with a slight irregularity of rhythm (Fig. 6 A). During this phase, no definite P-waves are to be found. Then P-waves reappear and are seen among the varying ventricular complexes, but complete dissociation between auricles and ventricles apparently exists (Fig. 6 B). At this point, all evidence of ventricular activity ceases, and for the space of about half a minute, nothing can be seen except irregularly spaced P-waves which have become inverted (Fig. 6 C). At the conclusion of the record, several bizarre ventricular complexes appear, all evidence of auricular

activity ceases, and the record ends with a regular series of ventricular complexes with deeply inverted T-waves, and a gradual change in the form of QRS (Fig. 6 *D*). The record ended approximately one to two minutes before the clinical death of the patient.

CASE 4.—D. J. was a 45-year-old housewife with mitral stenosis of long-standing, who entered the hospital for the second time because of cardiac insufficiency. During the two weeks before death, her course was one of progressive failure. She had a persistent slight fever but the heartbeat was slow and regular. An autopsy was not performed.

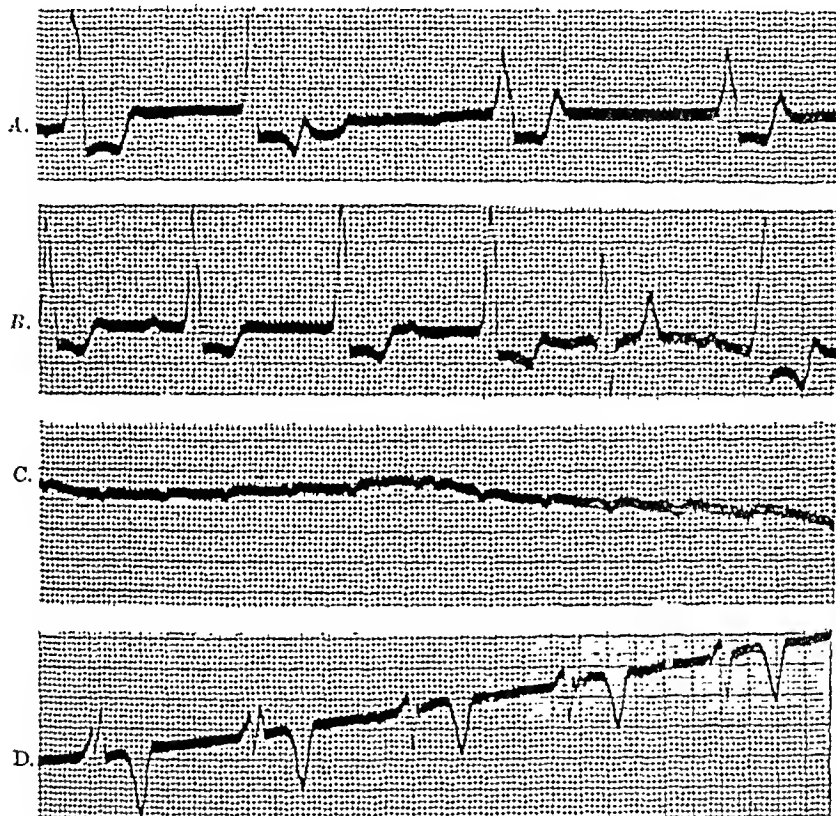


Fig. 6.—Case 3. About two minutes before clinical death. A, Lead I. B, Lead I. C, Lead II. D, Lead III.

Discussion of the Electrocardiograms.—The first electrocardiogram was taken four months before her death during her first admission to the hospital. It was characterized by marked “low voltage,” a rapid rate, right ventricular preponderance, and showed in addition an inversion of the T-wave in Lead III. In subsequent records the rate was slower and the voltage within normal limits. This was the case in the record taken at the time of her second admission two weeks before death. The only additional finding at this time was that T_2 as well as T_3 , had become inverted (Fig. 7).

The next electrocardiogram was started one to two minutes before clinical death. Marked irregularity of the sinus node is present. The P-waves are inconspicuous in the first lead but prominent and upright

in Leads II and III. The A-V conduction time is slightly prolonged. The intraventricular conduction time is 0.16 seconds and the ventricular complexes are bizarre in form, giving the picture commonly ascribed to block of the left bundle branch (Fig. 8).

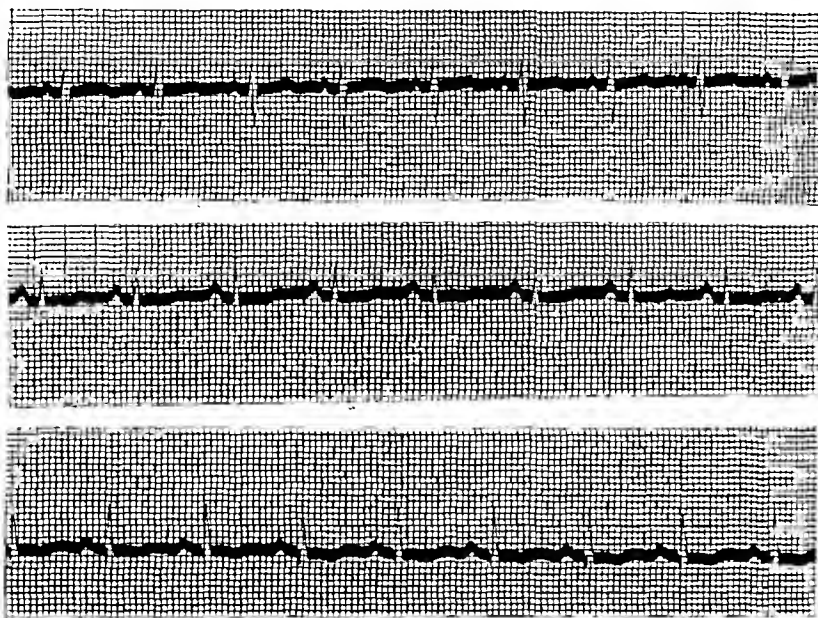


Fig. 7.—Case 4. Leads I, II, and III. Two weeks before death.

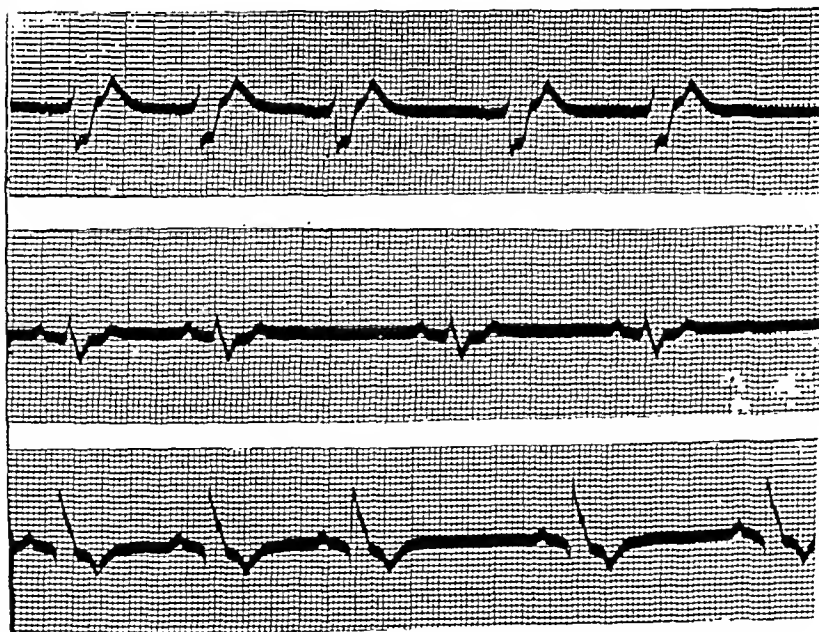


Fig. 8.—Case 4. Leads I, II, and III. About two minutes before clinical death.

The final record, taken during clinical death, shows a series of beats arranged in pairs resembling those in the previous Lead II. Occasional P-waves occur and are followed by ventricular complexes. These are seen in Fig. 9 A. In these sequences the P-R interval is 0.18 to 0.28 seconds.

The record was resumed after the lapse of a few seconds. All evidence of ventricular activity has disappeared. A few slight deflections from the base line are seen (Fig. 9 *B*). They probably represent auricular contractions. The rhythm is extremely irregular. Eventually all evidence of electrical activity ceases (Fig. 9 *C*).

CASE 5.—J. B. a 66-year-old white man had had increasing congestive heart failure for a year before admission. He was brought into the hospital in a moribund condition and died the day after admission.

Discussion of the Electrocardiograms.—The first record was taken about twenty-four hours before the death of the patient. It shows a sinus tachycardia with a rate of 120. Large numbers of auricular and

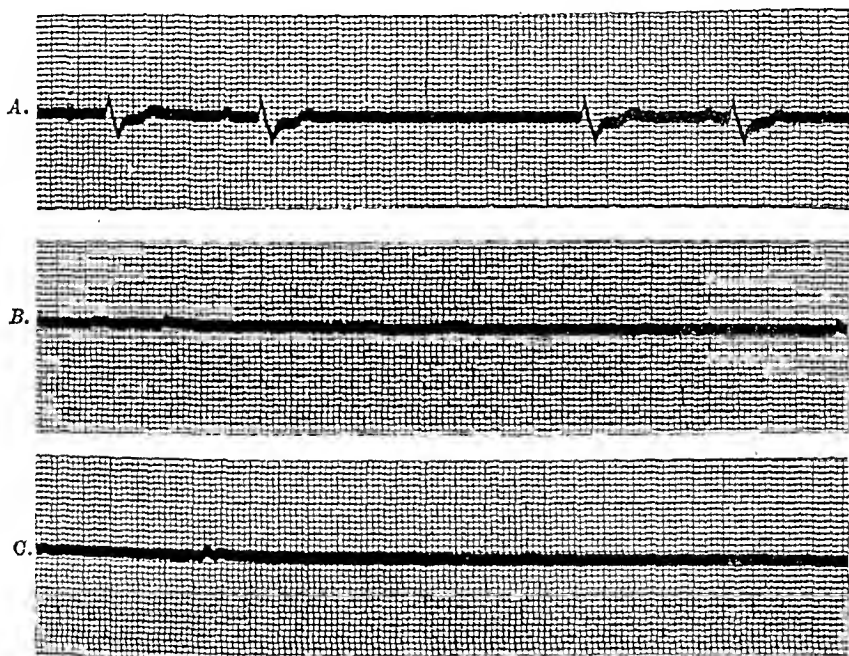


Fig. 9.—Case 4. A, Lead II. Approximately during clinical death. B, Lead II. A few seconds after the preceding. C, Lead II. End of cardiac activity.

nodal extrasystoles are present. The P-R interval is 0.12-0.14 sec. There is partial inversion of T_1 , while T_2 is iso-electric (Fig. 10).

Additional electrocardiograms were taken on the day of the patient's death which occurred at 3:00 P.M. Records were taken at 10:41 A.M., 10:47 A.M., 11:04 A.M., 11:45 A.M., 1:25 P.M., 1:35 P.M., and 2:15 P.M.

These all resemble the record of the previous day. The rate remains rapid, occasional auricular extrasystoles are seen, and there is no change in voltage or in conduction (Fig. 11 *A*).

The next electrocardiogram was begun at 2:55 P.M. which was five minutes before clinical death. In the forty minutes since the previous record the rate has become much slower—about 70 per minute (Fig. 11 *B*). The rhythm is regular and the sino-auricular node continues

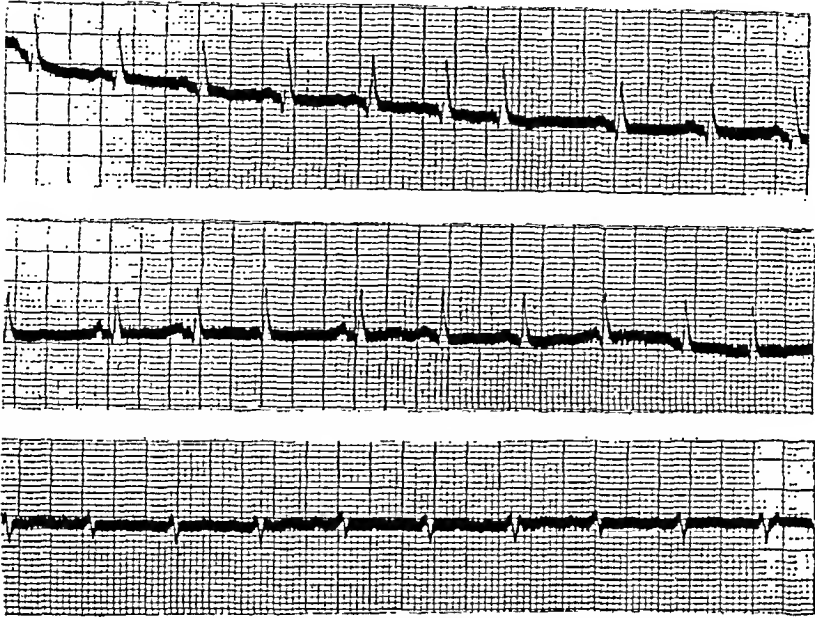


Fig. 10.—Case 5. Leads I, II, and III. About twenty-four hours before death.

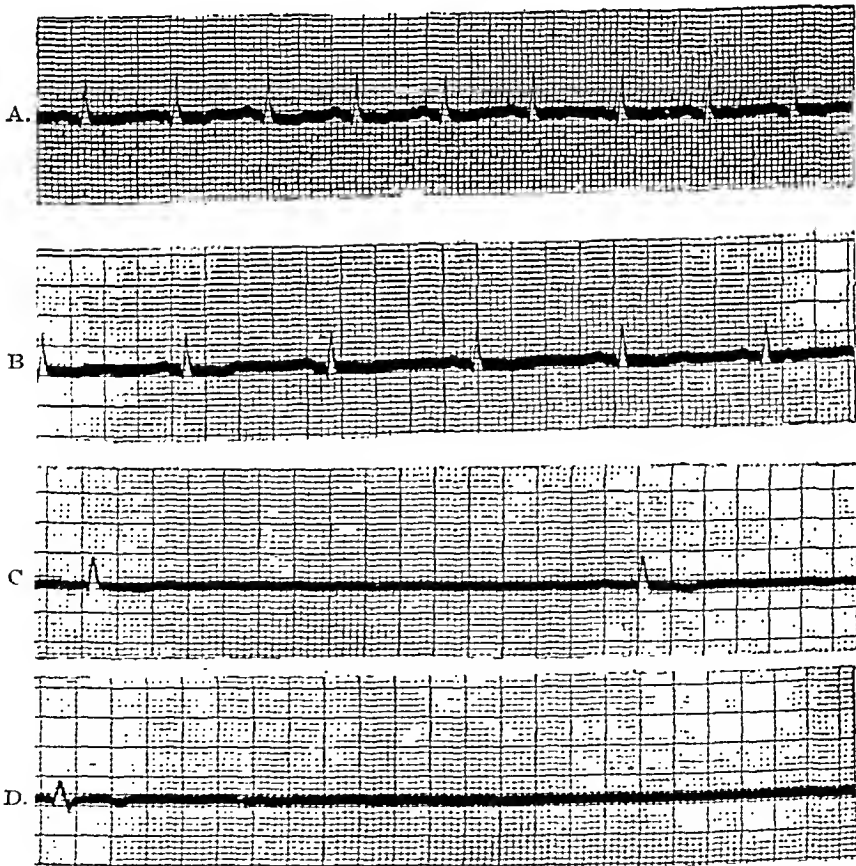


Fig. 11.—Case 5. Lead II. A, Taken at 2:15 P.M., about forty-five minutes before death. B, Four to five minutes before death. C, One minute after death. D, End of cardiac activity.

as the pacemaker. The P-R interval is still about 0.14 sec. Rare auricular extrasystoles are seen. At about this time clinical death occurred.

The record (Lead II) was resumed about a minute after death. The rate has now fallen to forty at the beginning of the record and grows gradually slower within the space of about ten seconds (Fig. 11 C). The P-waves at the beginning are upright. The conduction time is 0.24 sec. The R-wave is slurred, and the T-wave is inverted. As the rate slows, the P-waves diminish in amplitude and there seems to be a lengthening of the P-R interval, although this is very difficult to measure. Gradual slowing of the rate continues. Finally, after a series of beats coming quite regularly about three seconds apart, the heart stops beating for seventeen seconds, whereupon a single bizarre complex, probably of ventricular origin, is seen. Another pause of three or four seconds occurs, and cardiac activity is terminated by another bizarre complex (Fig. 11 D).

DISCUSSION

Electrocardiographic observations on the death of the human heart have been reported in sixty-five cases. To these the present series of five cases is added bringing the total to seventy. The three cases reported by Rohmer,² the twenty mentioned by Schellong,⁶ and two of the six included in Willius' paper⁷ are not susceptible to analysis because of insufficient data. This leaves forty-five cases that are reported in considerable detail.

There is a great variation in the mechanism of death of the human heart. This is the predominant impression that is to be gathered from a review of the cases reported in the literature. A conspicuous slowing of rate just before death is probably the most common finding. This is often associated with a change from normal sinus rhythm to an A-V nodal rhythm, but may occur without a change in the site of impulse formation. Marked slowing appeared in at least 70 per cent of the reported cases in which enough of the pertinent details were included. This figure is probably too conservative and would be larger if more data were given in the remainder of the cases. An excellent illustration of this decrease in rate is afforded by Case 5 in our series. Of nearly the same incidence (70 per cent) is the establishment of an A-V nodal or an idioventricular rhythm. However, aside from the slowing of the rate and the appearance of an A-V nodal rhythm, no other mechanism occurs sufficiently often to be predicted in a given case.

It is a common belief that ventricular fibrillation is the terminal mechanism in the majority of cases but this is not borne out by the electrocardiographic evidence. In about 20 per cent of forty-five cases ventricular fibrillation was the terminal event. In at least four other cases ventricular fibrillation was noted as a transient phenomenon. One

reason for the comparative infrequency of this finding may well be the fact that patients with ventricular fibrillation probably die suddenly in the majority of instances, whereas it is the cases with more gradual death that are susceptible to graphic study.

The age of the patient seems to play no part in determining the type of mechanism of the dying heart. Among the forty-five cases analyzed the age range is from nine months to eighty years. About 55 per cent were under forty years of age at the time of death. This group differed in no wise from the older patients in the types of terminal mechanisms recorded. From the data given, twenty of the forty-five patients may be classified as cardiac cases while the remaining twenty-five individuals died of causes other than heart disease. The mechanism of death in the two groups, divided on this basis, again shows no apparent difference. These facts have already been pointed out by Willius.¹¹ In other words, so far as the electrocardiographic manifestations during clinical death are concerned, it makes no difference whether the case be one of a child dying as the result of a pneumonia, or an old man dying because of a failing myocardium.

In order to make clinical application of our knowledge concerning the mode of cardiac death it is important not only to be able to recognize significant changes in the cardiac mechanism when they appear, but also to find these changes sufficiently in advance of death to afford an opportunity to apply therapeutic measures. An electrocardiogram is not needed to predict the death of the patient. It was obvious clinically, in most of the cases that have been reported, that the patient was dying, and therapeutic measures had been instituted before the electrocardiographer arrived to record the beats of the dying heart. In a few reported cases it is possible to determine the time before death when significant electrocardiographic findings were noted. Usually we are told that "just before the patient died" certain changes appeared. In most instances, therefore, these changes seem to precede clinical death by only a few minutes. This is illustrated in the series reported by Martini and Sekell¹⁰ who kept careful records of time relationships. In their first case, for example, tachycardia persisted up to five minutes before clinical death. Again, in the fifth case of the same series, the graphic records showed a tachycardia from four to six minutes before death with an A-V nodal rhythm appearing only a minute and a half *ante mortem*. In the fifth case in our series it was apparent that the patient was *in extremis* for nearly twenty-four hours. During the last five hours, death was expected momentarily. Yet the electrocardiogram did not show important changes until five minutes before clinical death. Hence it seems that the graphic record is of academic rather than of practical interest. Significant changes in the electrocardiograms appear so little ahead of death that the patient is usually dead before the film is developed.

SUMMARY

Sixty-five cases of electrocardiographic studies of the dying human heart reported in the literature are reviewed and five additional cases are recorded. Conspicuous slowing of the heart rate is the most frequent change in the mechanism of the heart which immediately precedes death. It has been found in over 70 per cent of the cases. Next in frequency is the appearance of an A-V nodal rhythm or an idioventricular rhythm. It is impossible to differentiate between the mechanism of cardiac death in patients with or without heart disease. The age of the patient likewise does not determine the manner in which the heart dies. Electrocardiographic studies of the dying human heart are, for the present at least, solely of academic value, as significant changes appear in the record only a very few minutes before clinical death.

REFERENCES

1. Hyman, A. S.: Resuscitation of the Stopped Heart by Intracardiac Therapy, *Arch. Int. Med.* 46: 553, 1930.
2. Rohmer: *München. med. Wchnschr.* 58: 2358, 1911.
3. Robinson, G. C.: A Study With the Electrocardiograph of the Mode of Death of the Human Heart, *J. Exper. Med.* 16: 291, 1912.
4. Halsey, R. H.: A Case of Ventricular Fibrillation, *Heart* 6: 67, 1915.
5. Dicouaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrhythmias. Report of Three Cases, *Arch. Int. Med.* 28: 663, 1921.
6. Schellong, F.: Elektrokardiographische Beobachtungen am sterbenden Menschen, *Ztschr. f. d. ges. exp. Med.* 36: 297, 1923.
7. Willius, F. A.: Changes in the Mechanism of the Human Heart Preceding and During Death, *Med. J. & Rec.* 119: supplement p. 49, 1924.
8. Reid, W. D.: Ventricular Ectopic Tachycardia Complicating Digitalis Therapy, *Arch. Int. Med.* 33: 23, 1924.
9. Kahn, M. H., and Goldstein, I.: The Human Dying Heart, *Am. J. M. Sc.* 168: 388, 1924.
10. Martini, P., and Seckell, J.: Das Sterben des menschlichen Herzens, *Deutsche Arch. f. klin. Med.* 158: 350, 1928.
11. Willius, F. A.: *Clinical Electrocardiograms*, Philadelphia, 1929, W. B. Saunders Co.
12. v. Hoesslin: Berlin letter, *J. A. M. A.* 96: 786, 1931.

VENTRICULAR FIBRILLATION WITH CARDIAC RECOVERY, CAUSED BY CAROTID SINUS PRESSURE, IN A CASE OF AURICULAR FIBRILLATION*

CHARLES SHOOKHOFF, M.D.

BROOKLYN, NEW YORK

WHILE there are relatively few recorded clinical cases of ventricular fibrillation, this arrhythmia is often mentioned as the cause of death in various types of disease; electrocution, coronary disease, chloroform poisoning, auricular fibrillation, paroxysmal tachycardia, other types of arrhythmia, etc. H. E. Hering,¹ drawing inferences from the frequent sudden death of experimental animals due to ventricular fibrillation, believes this arrhythmia a cause of death in patients who die suddenly and in whom, on pathological examination, no significant abnormalities are found.

Several cases of ventricular fibrillation with cardiac recovery have been recorded and reported by Kerr and Bender,² Levine and Matton,³ De Boer,⁴ Robinson and Bredeck,⁵ Hoffmann,⁶ and Dock.⁷

The case reported below is of interest not only because an electrocardiographic curve was obtained which is interpreted as being ventricular fibrillation, but because this arrhythmia occurred while doing a carotid sinus pressure test. The onset and cardiac recovery are recorded.

Czermak⁸ in 1866 described a slowing of the pulse rate caused by pressure over the right carotid artery and attributed this effect to a direct mechanical stimulation of the vagus. Hering,⁹ in his epoch-making researches, showed that the slowing of the cardiac rate and fall in systemic blood pressure are caused by pressure upon, or increased pressure within, the carotid sinus, a fusiform dilatation of the first portion of the internal carotid artery as it leaves the common carotid artery. He demonstrated that the sinus nerve, a branch of the glossopharyngeal, innervating the carotid sinus, is the pathway for reflexes causing the heart rate and blood pressure changes. De Castro's¹⁰ anatomical studies have corroborated Hering's conception of the innervation of the carotid sinus. He demonstrated that nerve filaments found in the sinus portion of the internal carotid artery only, joined nerve filaments arising in the carotid body, to make the inter-carotid nerve of De Castro (sensory) which enters the central nervous system principally through the ninth cranial nerve and to some extent through the vagal root ganglion.

*Department of Cardiology, the Jewish Hospital of Brooklyn.

Wenckebach has for many years used the "Vagusdruckversuch" in clinical medicine. The recent researches of C. Heymans^{11, 12, 13} and his coworkers, however, instigated by Hering's observations showing the importance of the influence of carotid sinus and depressor reflexes, rather than cerebral blood pressure changes, upon blood pressure, cardiac rate and control of adrenalin secretion, foreshadow changes in our concept of those diseases which cause, or are caused by, changes in blood pressure, cardiac rate and adrenal secretion. These studies are bringing the carotid sinus pressure test into more general clinical use.

During the course of a study on the clinical significance of the various types of reaction to carotid sinus pressure, many interesting electrocardiographic tracings were obtained by us. The electrocardiographic curves described below were recorded, while doing carotid sinus pressure tests, from a patient with severe myocardial disease and auricular fibrillation with a slow ventricular rate.

CASE REPORT

G. R. Male; aged 58 years; business man; born in the United States. Date of examination, November 20, 1930.

Family History.—Mother died at the age of 54 years, apoplexy; father died at the age of 60 years, heart trouble. One brother and one sister died in early adult life of pulmonary tuberculosis; two sisters and two brothers are well.

Past History.—Whooping cough; diphtheria; scarlet fever. No history of rheumatic fever or any of its manifestations. Married. Wife has four children; no miscarriages. Pneumonia at 31 years and typhoid fever at 35 years. Has had attacks of migraine and extrasystolic sensations since childhood. Venereal disease denied.

Present History.—Since the spring of 1930 patient has had signs and symptoms of cardiac impairment, dyspnea on exertion, swelling of the ankles, and subsequently nocturia and slight nocturnal dyspneic attacks. For the past six months he complains of a sense of constriction and pressure in his chest, radiating to the back, on walking. He had been told one year ago that he had high blood pressure.

Physical Examination.—Moderately well nourished male. Weight 174 lb.; height 75 in. Eyes react to light and accommodation. Eye grounds show retinal vessel sclerosis. Teeth—many extracted; pyorrhea alveolaris. No thyroid gland abnormalities. Chest—emphysematous; slight lateral curvature of the spine; occasional râles at both bases which clear up on deep breathing; no sacral edema. Temporal vessels tortuous and the walls palpable; radial vessel walls definitely thickened; brachial-vessel pulsations are visible. Heart—aortic configuration; left ventricle enlarged almost to the anterior axillary line; basilar vessel line is widened to the left; he has an auricular fibrillation with a slow ventricular rate. The highest systolic pressure was 180 and the lowest diastolic was 100 mm. Hg. A short blowing systolic murmur is heard at the apex; A-2 accentuated and musical; heart sounds poor and indistinct. Abdomen—rather prominent; liver enlarged two fingers below the costal margin. No fluid. Marked edema of the ankles, extremities otherwise normal; reflexes normal. Dorsalis pedis and posterior tibial pulsations present. Carotid sinus pressure on either the right or the left side causes a complete cardiac standstill during which time patient becomes extremely dizzy but not unconscious. At one time, however, he became bewildered for a short period. Fluoros-

copy:—Showed an aortic configuration with a very large left ventricle, a prominent aortic knob and a tortuous aorta; costophrenic sinuses are clear. Wassermann negative; uranalysis—trace of albumin, no sugar, specific gravity 1,020, urobilinogen present; blood chemistry normal.

Diagnosis.—Essential hypertension; coronary vessel sclerosis; myofibrosis cordis; cardiac decompensation; retinal and radial vessel sclerosis; auricular fibrillation; chronic bronchitis and emphysema.

Subsequent History.—Patient improved on rest, cardiac tonics and diuretics. Has had no subsequent attacks and is up and about at the time of this report.

Electrocardiographic Studies.—(Taken on the day of examination.) Fig. 1 shows an auricular fibrillation with an average ventricular rate of 66. Left axis deviation. In Lead I the R-T interval is depressed

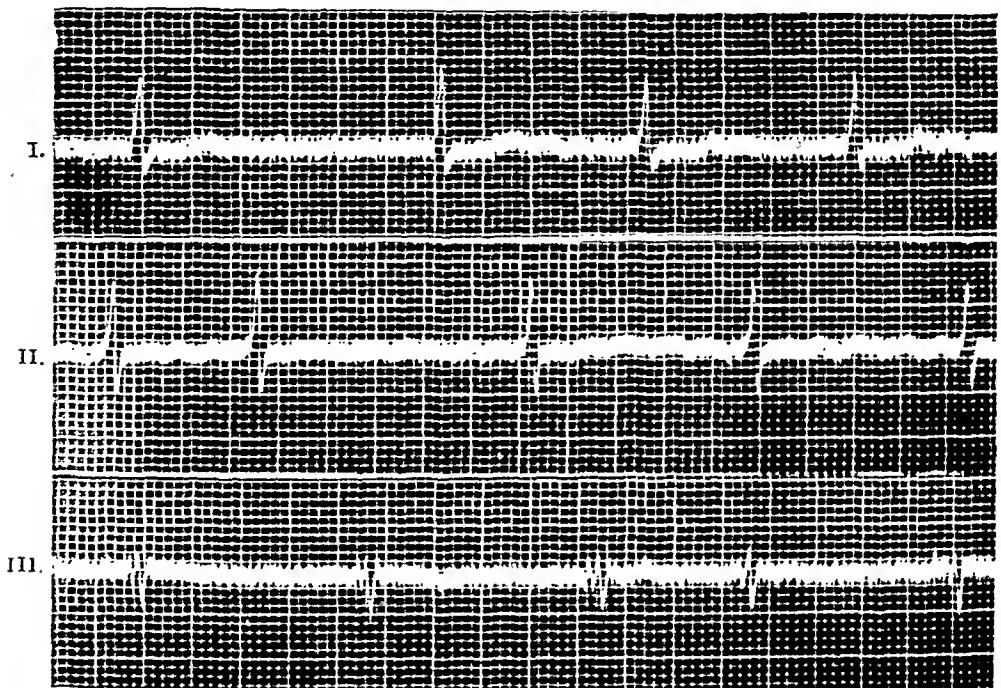


Fig. 1.—Auricular fibrillation, average ventricular rate 66. T-wave changes and slurring of the main deflections indicative of myocardial involvement.

below the isoelectric line. In Leads II and III the T-waves are isoelectric. The main deflections in all leads are slightly slurred.

Reaction to Carotid Sheath Pressure.—Fig. 2 (Lead III) shows the effect of left carotid sinus pressure. An absence of supraventricular complexes for a period of 8.68 seconds is noted. This period is interrupted by two aberrant ventricular complexes, one coming after a period of cardiac inactivity of 2.92 seconds and the other one following after 3.68 seconds. The aberrant ventricular complexes may be either right bundle-branch block or, more likely, ventricular extrasystoles. In the long periods of ventricular inactivity there is no change in conformation of the isoelectric line.

Fig. 3 (Lead III) was obtained as pressure was exerted upon the right carotid sinus. The S-wave is of low voltage and is the main de-

flection; auricular fibrillation is present. Carotid sinus pressure is made at the arrow; almost immediately following is a series of irregular movements of the isoelectric line at slightly varying rates, approximately 225 per minute. The first few complexes look like aberrant ventricular beats (A-B) and are similar in shape and direction to extrasystoles arising at the base of the ventricle. Then follows a period (B-C) of irregular movements of the isoelectric line showing no definite ventricular conformations. This is subsequently followed by a series of regular undulations of wider amplitude (C-D) and similar in shape and direction to extrasystoles arising at the apex of the left ventricle. A return to the original status, auricular fibrilla-

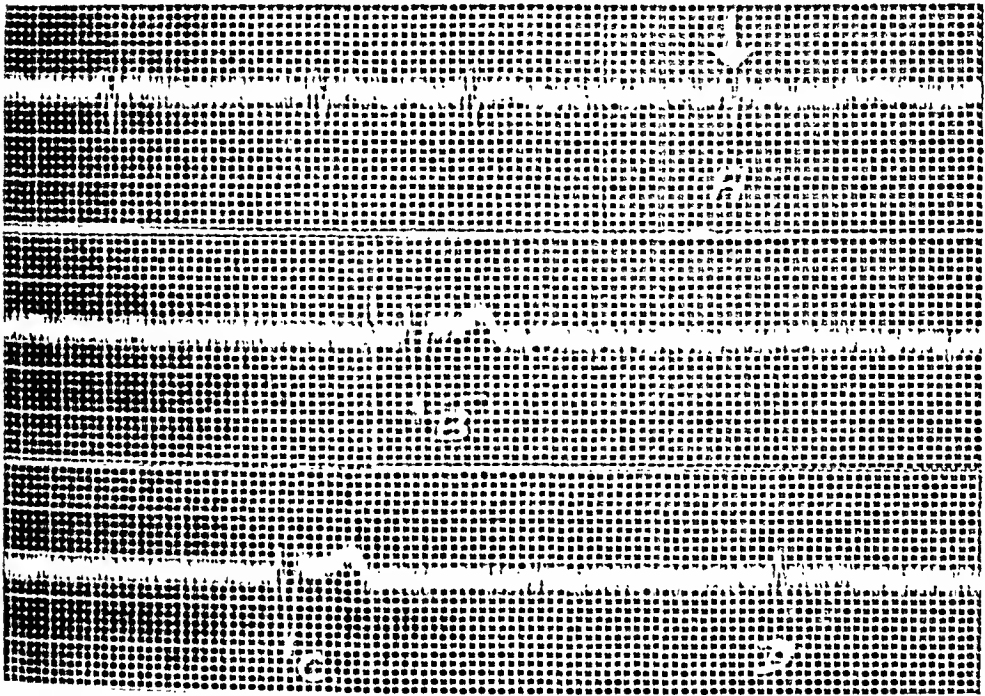


Fig. 2.—These are continuous strips of Lead III showing long pauses and aberrant ventricular complexes caused by pressure on the left carotid sinus (arrow). Time between supraventricular beats "A" and "D" is 8.68 seconds; between "A" and aberrant ventricular beat "B" is 2.92 seconds, and between "B" and aberrant beat "C" is 3.68 seconds.

tion, is now seen. This period of irregularity extends over a period of 8.68 seconds. Occasional complexes are seen which appear to be sinus beats (S). These complexes are not preceded or followed by pauses. No isoelectric period is seen in the tracing from "A" to "D."

During this time the patient became very dizzy, was bewildered for a few seconds and then became normal again.

DISCUSSION

A proper discussion and evaluation of the above findings necessitate answering the following questions: 1. Does carotid sinus pressure cause a reflex vagal stimulation? 2. Does carotid sinus pressure cause

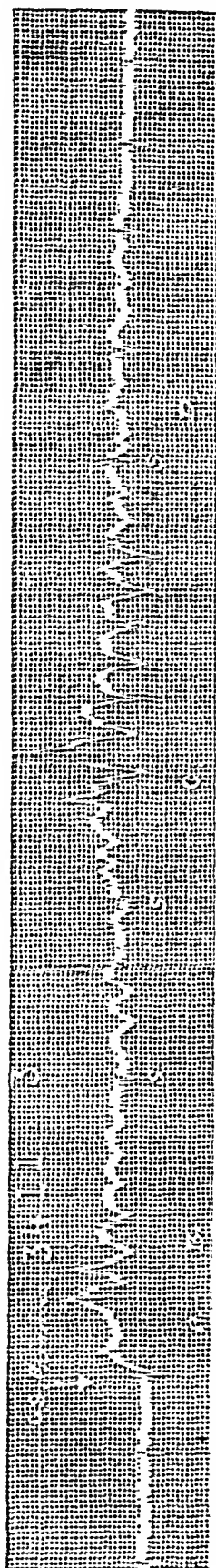


Fig. 3.—This arrhythmia was caused by pressure on the right carotid sinus (arrow). A-B and C-D are periods of ventricular activity which appear like successions of aberrant ventricular beats arising at the base and at the apex respectively. B-C is similar to Halsey's tracing of ventricular fibrillation. "S" indicates possible supraventricular complexes.

ventricular rate changes in auricular fibrillation, since in this arrhythmia the sinus is not the pacemaker? 3. What effect has vagal stimulation upon lower automatic centers in ventricular musculature? 4. Does Fig. 3 represent ventricular fibrillation?

1. Hering's and Heymans' investigations, as well as De Castro's anatomical studies, have shown that compression of the carotid sinus causes a reflex vagal stimulation.

2. Kronecker and Spallitta¹⁴ in 1905, showed, in animals, that vagal stimulation slows the ventricular rate during auricular fibrillation. Robinson,¹⁵ Fahrenkamp,¹⁶ and Semeran,¹⁷ and others have caused a ventricular slowing in patients with auricular fibrillation by pressure on the carotid sheath. Boas¹⁸ by means of his tachometer, has shown that the ventricular rate in patients with auricular fibrillation is influenced by the same factors which influence ventricular rates in normal individuals, i.e., rest, sleep, excitement, etc. The slowing of the ventricular rate by carotid sinus pressure is due to the reflex stimulation of that part of the vagal mechanism which has its preponderant influence upon the A-V connecting system. By depressing the conductivity of the bundle it decreases the number of impulses conducted to the ventricle. Changes in cardiac rate in normal individuals are dependent upon changes in tone of the vagus and sympathetic which control the rate of impulse formation in the sinus.

3. While fibers of the sympathetic system are known to exist in all parts of the heart muscle, definite proof of the presence of vagus fibers in the ventricular musculature has not been forthcoming. Drury¹⁹ has shown that vagal stimulation does not decrease the refractory period of ventricular musculature in experimental animals, and Lewis²⁰ states that the vagus has little effect on ventricular musculature. Rothberger and Winterberg²¹ have shown that the fibrillation rate in the ventricle is not influenced by vagal stimulation.

On the other hand, both Hering¹ and Winterberg²² were of the opinion that stimulation of the vagus caused lower ventricular centers to become hyper-irritable only indirectly; that its action was that of furthering only the occurrence of these arrhythmias. Hering¹ maintains that vagal stimulation depresses the force of ventricular contractions as well as conduction through ventricular musculature.

Hering¹ further states that not only electrical vagal stimulation, but vagal stimulation by breathing, etc., reflexly from the carotid sinus, from mucous membranes, etc., have the same influence upon ventricular musculature. Smith and Moody²³ reported cases in which premature contractions and idioventricular rhythms were induced by forced breathing.

Knoll²⁴ in 1897 caused all sorts of ventricular arrhythmias by vagal stimulation, including ventricular fibrillation, in curarized rabbit hearts. Rothberger and Winterberg²¹ have, by vagal stimulation,

caused similar arrhythmias in dogs and cats which were previously administered barium chloride, chloroform and other drugs. Scherf,²⁵ by stimulating the right vagus, caused many ventricular extrasystoles and other aberrant ventricular arrhythmias in dogs to whom aconitine had been administered.

Kisch²⁶ in 1921 produced in animals a greater tendency to heterotopic ventricular arrhythmias by clamping both carotids. Many ectopic ventricular rhythms have been recorded by us (to be reported) and by others while doing the carotid sinus pressure test. It is found that these arrhythmias occur more readily in patients who have severely damaged ventricular musculature. Digitalis causes idioventricular rhythms, especially in persons with diseased heart muscle. Latent bigeminal rhythms in well digitalized patients are sometimes brought out by carotid sinus pressure.

All these data seem to justify the impression that while normal ventricular musculature appears not to respond to vagal stimulation, diseased ventricular musculature, diseased by whatever cause, does respond to such stimulation by all sorts of ectopic idioventricular rhythms.

Braun and Samet²⁷ have shown that the effect of carotid sinus pressure, was markedly increased in cats, when branches, particularly of the left coronary arterial system, were tied.

It seems that a vicious circle is established in patients with severe myocardial disease, for not only does diseased ventricular musculature respond by the occurrence of idioventricular rhythms to vagal stimulation, but, as Braun and Samet have shown, and as has been noticed in the clinic, damage of ventricular musculature increases the irritability of the vagus.

4. The curves of ventricular fibrillation recorded, obtained both from experimental animals and human beings, are of various types. They seem to have the same relationship to each other, as do the various types of the auricular circuit movement arrhythmias, i.e., auricular flutter, with its regular auricular contractions at the rates of approximately 300 per minute; impure flutter or coarse fibrillation at higher and irregular auricular rates; and auricular fibrillation with its very high fibrillation rate, marked irregularity, dilatation of the auricle, and failure of coordinated auricular contractions. De Boer¹ and Rothberger and Winterberg²¹ have described these various types of ventricular fibrillation. Lewis²⁰ has described various stages of ventricular fibrillation in experimental animals. The early stage of frequent premature ventricular contractions, followed by the stage of more or less regular movements of the isoelectric line (up to this time no dilatation of the ventricle has taken place), and finally tremen-

dously increased irregular ventricular circuit movement rates with a dilatation of the ventricle and an absence of coordinated ventricular contractions.

It seems to us that the curves of ventricular fibrillation described as flutter and impure flutter are really aborted stages of what ultimately might have been that stage of ventricular fibrillation which parallels auricular fibrillation. These stages or aborted types, if we may use that term, are exemplified by the following curves—the flutter stage or type, by Kerr and Bender's² first portion of Fig. 8; Dock's⁷ curves, Fig. 2; De Boer's⁴ and Hoffmann's,⁶ etc.; and the impure flutter stage, by our Fig. 3. The fibrillation stage is exemplified by Kerr and Bender's² Fig. 9. Lewis characterizes Hoffmann's tracing and others like it as potential ventricular fibrillation.

In the auricular-circuit-movement arrhythmias transition from one type to another are not infrequent, particularly when quinine or digitalis has been given. There seems to be a greater tendency of transition from one stage or type to another in the ventricular circuit movement arrhythmias.

Fig. 3, at the onset (A-B) and toward the end (C-D), is similar to Dock's⁷ curves taken from a patient in whom syncopal attacks were induced by adrenalin; to De Boer's⁴ taken from a patient with complete heart-block, and which he described as ventricular flutter and fibrillation, showing at times a short series of ventricular aberrant beats; to Hoffmann's⁶ curve obtained at the end of an attack of paroxysmal tachycardia before the establishment of a sinus rhythm, which he called ventricular fibrillation and which Lewis calls potential ventricular fibrillation; and to the curves of Rothberger and Winterberg's²¹ Plate V, Fig. 13-a, obtained from a dog. For a short distance (B-C) in our curve, the rapid irregular undulations of the isoelectric line are different from those seen in parts of the curve A-B and C-D. This part (B-C) of Fig. 3 is similar to Halsey's²⁸ curve obtained from a patient dying of pneumonia.

This arrhythmia begins with ventricular aberrant beats immediately following carotid sinus pressure, goes into a ventricular circuit movement, returns again to aberrant ventricular coordinated beats and then to the previous status. We think that this curve represents activity in the ventricle which parallels the auricular arrhythmia called impure flutter or coarse fibrillation in the auricle. It represents an aborted ventricular fibrillation.

It seems that this patient had all the possible factors necessary for the occurrence of an ectopic ventricular arrhythmia. He had suffered from migraine and had extrasystoles for many years; thus supplying the possible developmental factor. Wittgenstein²⁹ believes that the occurrence of aberrant rhythms, paroxysmal tachycardias, is an indication of an exudative diathesis. Patient developed a myofibrosis

cordis, supplying the myocardial disease factor, and an auricular fibrillation with a slow ventricular rate, not dependent upon digitalis—indicating some degree of organic A-V block—supplying the factor that Davis and Sprague³⁰ believe necessary for the occurrence of aberrant ventricular circuit movement rhythms.

All these underlying factors being present, carotid sinus pressure stimulating a vagal system made hyper-irritable by diseased ventricular musculature caused the aborted ventricular fibrillation.

SUMMARY

The occurrence of a ventricular fibrillation upon carotid sinus pressure with spontaneous cardiac recovery is reported in a patient with auricular fibrillation, who had signs and symptoms of severe myocardial degeneration.

The newer physiology of the carotid sinus pressure test and its relationship to clinical medicine are briefly mentioned. The pathological physiology of ventricular-rate changes by vagal stimulation in auricular fibrillation is described and the effect of vagal stimulation upon lower automatic centers in ventricular musculature is discussed.

It is suggested that the occurrence of ventricular fibrillation in this patient is additional evidence in support of the concept that vagal stimulation, from whatever cause, will produce idioventricular arrhythmias in diseased ventricular musculature.

REFERENCES

1. Hering, H. E.: *Der Sekundenherztod mit besonderer Berücksichtigung des Herzkammerflimmerns*, Berlin, 1917, Julius Springer.
2. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart-Block While Under Quinidine Sulphate Therapy, *Heart* 9: 269, 1921.
3. Levine, S. A., and Matton, M.: Observations on a Case of Adams-Stokes Syndrome Showing Ventricular Fibrillation and Asystole Lasting Five Minutes With Recovery Following the Intra-Cardiac Injection of Adrenalin, *Heart* 12: 271, 1926.
4. De Boer, S.: Ueber Kammerflattern und Kammerflimmern bei einem Patienten mit totalem Herzblock, *Ztschr. f. d. ges. exper. Med.* 38: 191, 1923.
5. Robinson, G. C., and Bredeck, J. H.: Ventricular Fibrillation in a Man With Cardiac Recovery, *Arch. Int. Med.* 20: 725, 1917.
6. Hoffmann, A.: Fibrillation of the Ventricle at the End of an Attack of Paroxysmal Tachycardia in Man, *Heart* 3: 213, 1911-1912.
7. Dock, W.: Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulphate, *AM. HEART J.* 4: 709, 1929.
8. Czernak, J.: Ueber Mechanische Vagusreizung beim Menschen, *Jen. Ztschr. f. Med. u. Naturw.* 2: 384, 1866.
9. Hering, H. E.: *Die Karotissinusreflexe auf Herz und Gefässe*, Dresden and Leipzig, 1927, Theodor Steinkopff.
10. De Castro, F.: Sobre la fina Anatomía de los Ganglios Simpáticos, Vertebrales y Paravertebrales de los Simios, *Arch. de neurobiol.* 7: 38, 1927.
11. Heymans, C.: The Control of Heart Rate Consequent to Changes in the Cephalic Blood Pressure and in the Intra-cranial Pressure, *Am. J. Physiol.* 85: 498, 1928.
12. Heymans, C.: Ueber die Physiologie und Pharmakologie des Herz-Vagus-Zentrums, *Ergebn. d. Physiol.* 28: 244, 1929.

13. Heymans, C.: Le Sinus carotidien, *Arch. Internat. de Pharmacod. et de Therapie*, 35 (fascicule iii): 269, 1929.
14. Kronecker, H., and Spallitta, F.: La Conduction de l'Inhibition à travers le Cœur du Chien, *Arch. internat. de physiol.* 2: 223, 1904.
15. Robinson, G. C.: The Influence of the Vagus Nerves on the Faradized Auricles in the Dog's Heart, *J. Exper. Med.* 17: 429, 1913.
16. Fahrenkamp, K.: Klinische und elektrographische Untersuchungen über die Einwirkung d. Digitalis u. d. Strophanthins a. d. insuffiziente Herz, *Deutsches Arch. f. klin. Med.* 120: 11, 1916.
17. Semberan, M.: Die Flimmerarrhythmie. *Ergebn. d. inn. Med. u. Kinderh.* 19: 134, 1921.
18. Boas, E. P.: The Ventricular Rates in Auricular Fibrillation Studies With the Cardiotachometer, *AM. HEART J.* 4: 499, 1929.
19. Drury, A. N.: The Influence of Vagal Stimulation Upon the Force of Contraction, and the Refractory Period of Ventricular Muscle in the Dog's Heart, *Heart* 10: 405, 1923.
20. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, Shaw & Sons, Ltd.
21. Rothberger, J., and Winterberg, H.: Das Flimmern der Herzkammern, Weiterer Beitrag zur Pathogenese des Flimmerns, *Ztschr. f. d. ges. exper. Med.* 4: 407, 1916.
22. Winterberg, H.: Studien über Herzflimmerns, *Pflüger's Arch. f. d. ges. Physiol.* 117: 223, 1907.
23. Smith, F. M., and Moody, W. B.: The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, *Arch. Int. Med.* 32: 192, 1923.
24. Knoll, Ph.: Ueber die Wirkung des Herzvagus bei Warmblütern. *Pflüger's Arch. f. d. ges. Physiol.* 67: 587, 1897.
25. Scherf, D.: Wirkung der Herznerven auf die Reizbildung in der Kammer, *Wien. klin. Wchnschr.* 41: 1769, 1928.
26. Kisch, B.: Die Förderung der Heterotopen Herzreizbildung durch Verschluss der Karotiden, *München. med. Wchnschr.* 68: 1317, 1921.
27. Braun, L., and Samet, B.: Zur Klinischen Bedeutung des "Vagusdruckes," *Wien. klin. Wchnschr.* 40: 1382, 1927.
28. Halsey: A Case of Ventricular Fibrillation, *Heart* 6: 67, 1915.
29. Wittgenstein: Exudative Diathese und Vegetatives Nerven System, *Wien. Arch. f. inn. Med.* 9: 417, 1925.
30. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relationship to Heart-Block, *AM. HEART J.* 4: 559, 1929.

UNUSUAL VARIATIONS OF THE ROENTGEN SHADOW OF THE ELONGATED THORACIC AORTA

HUGO RÖSLER, M.D.

VIENNA, AUSTRIA

AND

PAUL D. WHITE, M.D.

BOSTON, MASS.

INTRODUCTION

THE x-ray appearance of the tortuous aorta is well known. In the anteroposterior view the supracardiac shadow is widened on both sides. The intersection between the right auricular border and the ascending portion of the aorta is rather low. The latter is more prominent, its outline being more curved than usual. On the left, the aortic knob is highly situated and prominent. Its shape and size depend upon the further course of the descending aorta; this vessel may be situated anteriorly to the vertebral bodies or more to their left. In the latter case, the descending aorta is unusually well visualized and may disappear behind the heart shadow in the region of the auriculo-ventricular junction and not as usually within the *conus pulmonalis*. The outline of this descending vessel is either straight or slightly curved, the convexity being directed to the left. In films taken with higher voltage and sufficient exposure or in films where the Potter-Bucky diaphragm is used, the shadow of the descending aorta is easily seen through the heart shadow and is always seen partly to the left of the midline. In the left anterior oblique position the entire loop of the aorta is seen, and the type of curve resembles rather more that of a circle than that of an ellipse or of an even more sharply kinked curve as we see it in normal conditions, but the circumference of the curve always remains smoothly outlined. In the right anterior oblique position there is no very characteristic picture, part of the descending aorta or sometimes the entire vessel being seen within the retrocardiac space. This type of aorta is found usually, although not always, in old people and in patients with arteriosclerosis and hypertension.

CASE REPORTS

In the following four cases of arteriosclerosis an unusual course of the descending aorta has been observed.

CASE 1.—The first case, Massachusetts General Hospital, X-ray No. 66530, June 20, 1927, was a carpenter, 60 years of age. He had suffered for years from an

arthritic condition of the knee. There were no other complaints. The Wassermann reaction was repeatedly positive. X-ray examination showed definite calcification of the popliteal artery on each side. The caliber of the left popliteal artery was about three times the normal—probably due to an aneurysm. Clinical examination revealed essentially normal heart findings. The aortic second sound was accentuated. The blood pressure was 160 millimeters of mercury systolic and 95 millimeters diastolic.

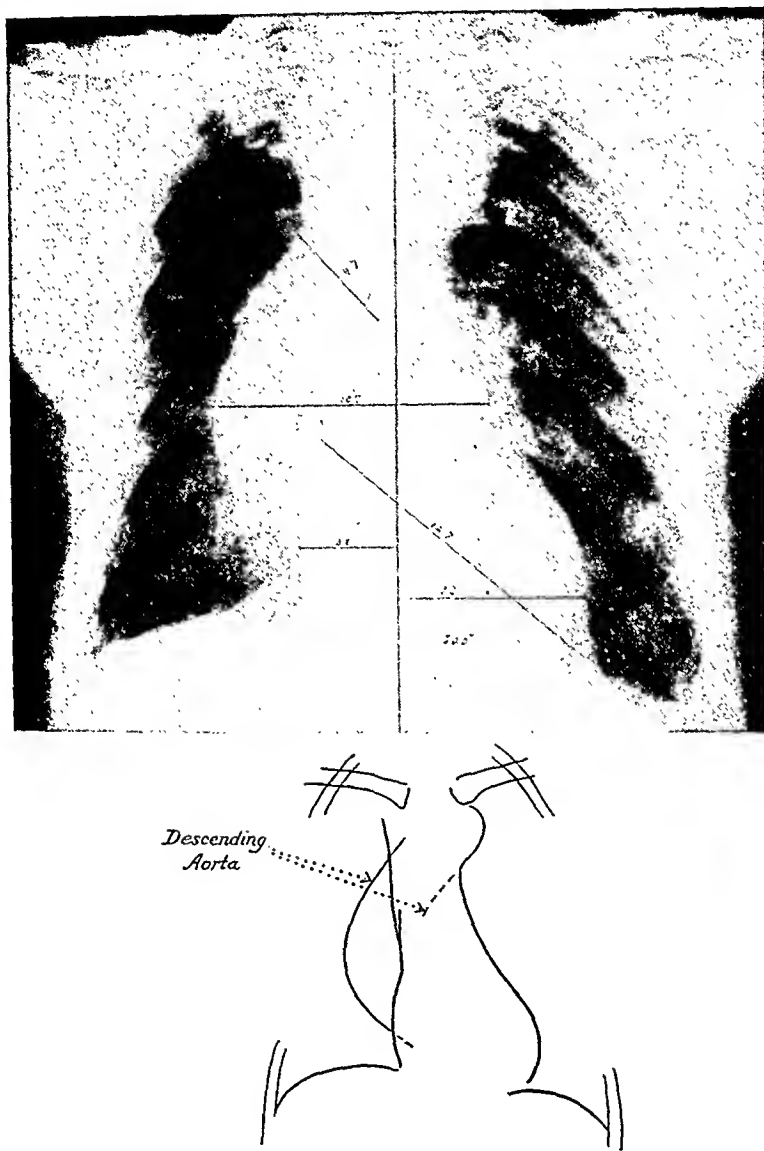


Figure 1—Roentgenogram, anteroposterior view, Case 1.

An x-ray film of the chest, anteroposterior view (Fig. 1), showed the heart to be normal in size and shape (transverse diameter 11 cm., internal diameter of chest 25.5 cm.). The supracardiac shadow was markedly enlarged, measuring 10.7 cm. The aortic knob was high to the left. The descending aorta turned in its course sharply toward the median line, its left contour being well seen, crossing the vertebrae into the right lung field. Its contour can be followed downward and medially to disappear within the right auricular shadow. In the right

anterior oblique view (Fig. 2) the trachea is seen to be displaced forward at the height of the aortic arch.

It is obvious that the aortic shadow seen in the anteroposterior view in the right lung field was caused by the descending aorta. This vessel shows a marked S-like curve directed posteriorly and to the right

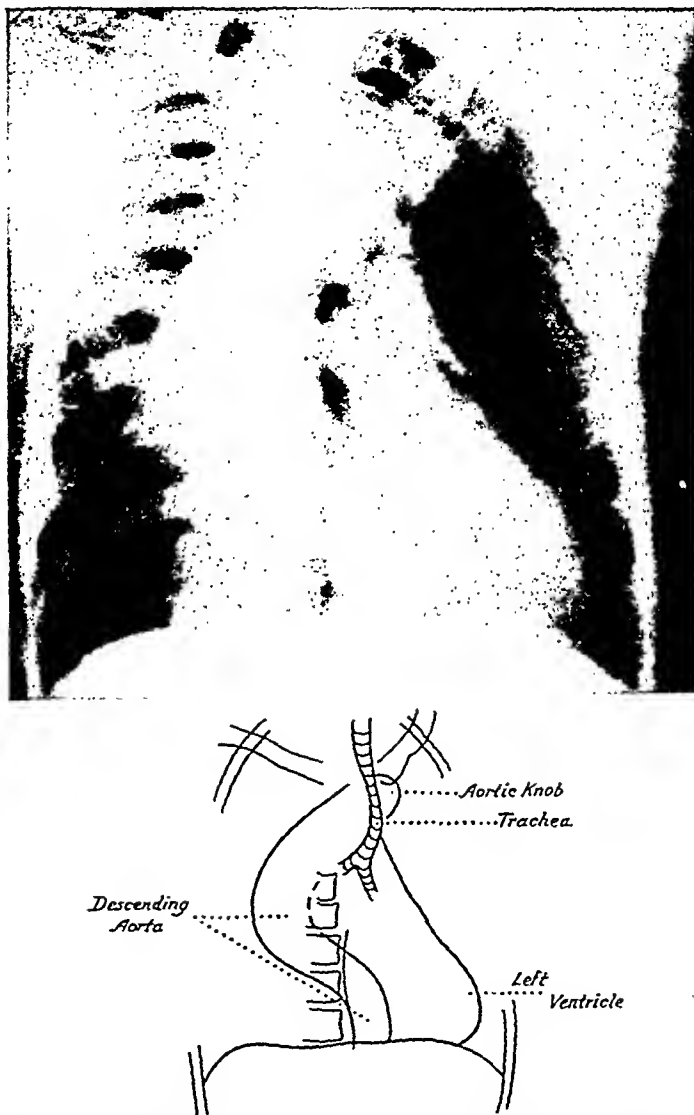


Figure 2—Roentgenogram, right anterior oblique view, Case 1.

in its upper part and forward and to the left in its lower part. The anterior and posterior portions are well visualized. The distinctness of the shadow makes it possible to establish a correct measurement of the width of the aorta: 5 cm. for the upper portion and 4 cm. for the lower. The right oblique view shows no shadow of the descending aorta overlying the vertebrae. Anteriorly in this view, the normal rather flat curved border of the ascending aorta is seen. The course of the aortic vessel can therefore be described as follows: The ascend-

ing aorta and arch are relatively normal. The descending aorta crosses the midline, thus displacing the trachea forward, bulges broadly into the posterior right lung field, and returns behind the heart to the midline.

Two findings are remarkable. First, the displacement of the trachea anteriorly has been known up to the present to occur with one

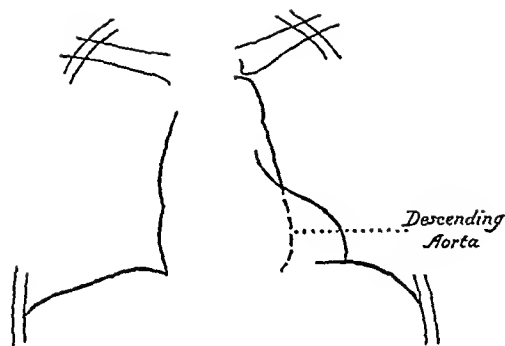


Figure 3—Roentgenogram, anteroposterior view, Case 2.

other condition only, namely, the right sided aortic arch. With that congenital anomaly, the aortic arch turns behind the trachea and esophagus to the right of the midline. All cases of that anomaly which have been studied, however, have shown a very characteristic finding, the absence of the aortic knob on the left and a displacement of the trachea to the left at the height of the aortic arch. Neither of these findings is present in our case. Therefore, the diagnosis of this anomaly has to be discarded.

Second, the degree of curvature of the descending aorta is striking. One must assume that the left intercostal arteries have undergone a considerable lengthening. In using only the anterior view one might be tempted to diagnose an aneurysm of the ascending portion of the aorta. The best explanation for the abnormal course of the aorta is

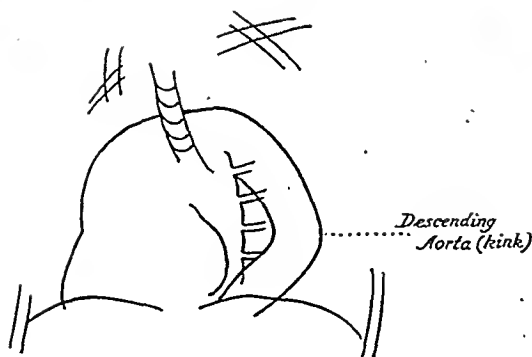


Figure 4—Roentgenogram, left anterior oblique view, Case 2.

the conception that the vessel has become too long between its two points of fixation, the heart and the diaphragm. We know that the process of arteriosclerosis affects chiefly the descending portion of the aorta. Syphilis, though present in this case, cannot account for the aortic anomaly.

CASE 2.—The second case, Massachusetts General Hospital, X-ray No. 132754, January 29, 1931, was a male, 61 years old, who worked as a butler. Fourteen years before, a diagnosis of early tabes was made. The Wassermann reaction was repeatedly positive. He suffered from attacks of shooting girdle pain. There were

no complaints suggesting heart disease. Some years before the date noted above, the heart findings had been essentially negative. The only abnormal circulatory finding that had developed since was slight hypertension, the systolic blood pressure being 160 millimeters of mercury.

In an x-ray of the chest, anteroposterior view (Fig. 3); the heart showed an "aortic configuration" but its size was within the limits of

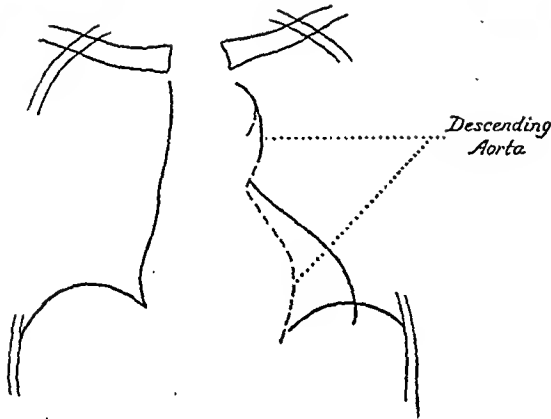


Figure 5—Roentgenogram, anteroposterior view, Case 3.

normal (transverse diameter 13.8 cm., internal thoracic diameter 30 cm.). The aortic shadow was moderately widened and showed calcification. Its course is seen through the heart shadow as it curves medially above the diaphragm. In the left anterior oblique view (Fig. 4) the descending aorta is well seen in its entire course as a rather dense band of about 3.7 cm. in diameter. Its upper two-thirds are directed downward and slightly backward, its lower third markedly forward, thus forming a kink. In the anteroposterior view only, it would be

difficult to differentiate this abnormality from a fusiform aneurysm of the lower portion of the descending aorta, an appearance which the oblique view conclusively demonstrates as being due to the wide course of the aorta. This aortic deformity is explained by elongation of the aorta, so that kinking is necessary to allow it to fit into the

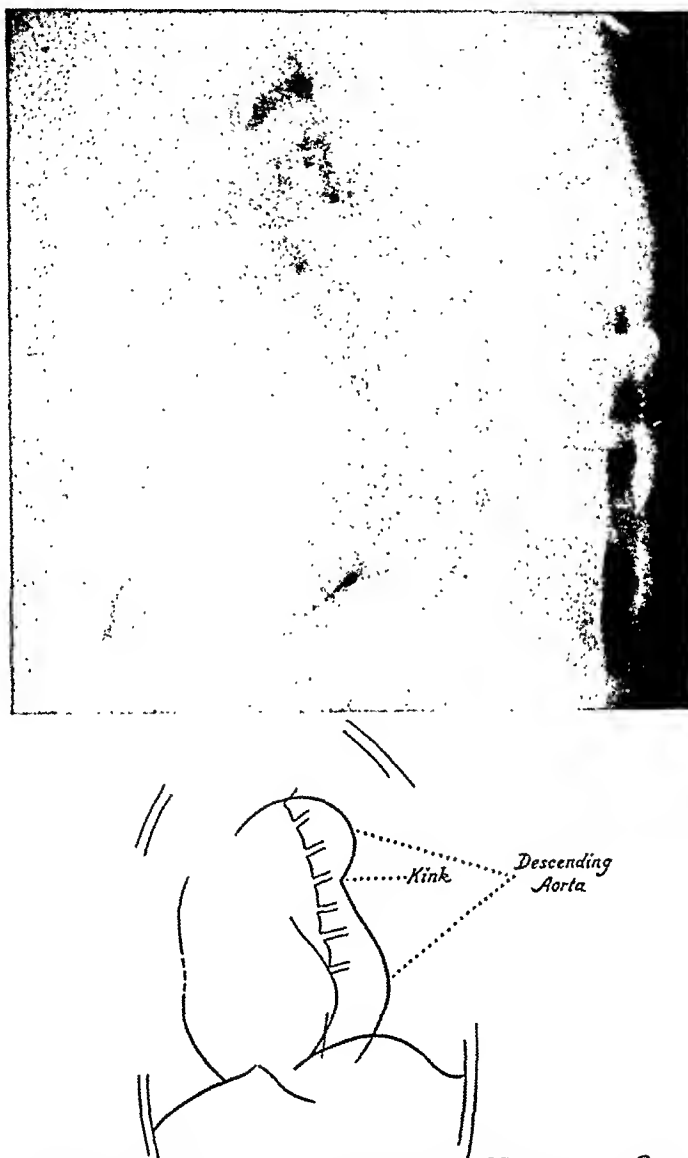


Figure 6—Roentgenogram, left anterior oblique view, Case 3.

thorax. Atherosclerosis causes such elongation; luetic aortitis may or may not be a factor underlying the atherosclerosis.

CASE 3.—The third case, Massachusetts General Hospital, X-ray No. 189542, December 13, 1930, was a male, 50 years old, who worked as a carpenter. For six months he had been suffering from headache, vertigo, and transitory scotomas. The heart was slightly enlarged to the left. The aortic second sound was accentuated. The blood pressure was 220 mm. mercury systolic and 118 mm. diastolic, later 170 mm. systolic and 90 mm. diastolic. The Wassermann reaction was negative. The radial and brachial arteries were tortuous. There were no clinical signs of coarctation of the aorta. The diagnosis was essential hypertension.

In an x-ray film of the chest, anteroposterior view (Fig. 5), the heart shows an aortic configuration and moderate enlargement (transverse diameter 16 cm., internal thoracic diameter 30.7 cm.). The aortic knob is prominent. The left border of the descending aorta below the aortic knob bulges considerably. Below the level of the left bron-

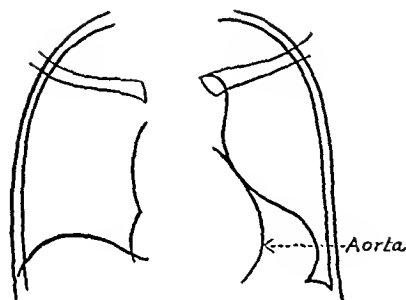
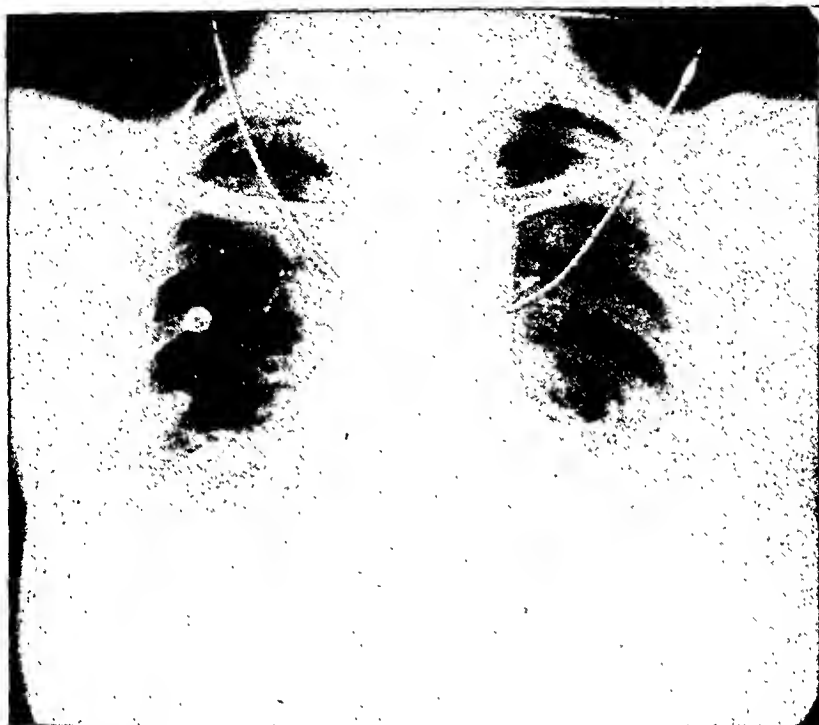


Figure 7—Roentgenogram, anteroposterior view. Case 4.

chus within the heart shadow, there is a definite indentation. In the left anterior oblique view (Fig. 6) at the upper portion of the descending aorta below the arch, the outer border of the aortic shadow shows a marked indentation, the course of the entire vessel undergoing a sudden change in direction. In the absence of a well defined anterior border in almost the entire course of the aorta, no measurement can be made, but for a short distance above the diaphragm where the anterior border is visible, the aorta shows narrowing in its downward course and some calcification is seen. In this case, the indentation below the aortic

arch best seen in the oblique view might suggest a real narrowing such as is present in coarctation of the aorta. The lower margins of the posterior ribs, however, do not show the erosions seen in this disease and no clinical evidence of this anomaly is present. As the inner and anterior contour of the lower portion of the descending aorta could

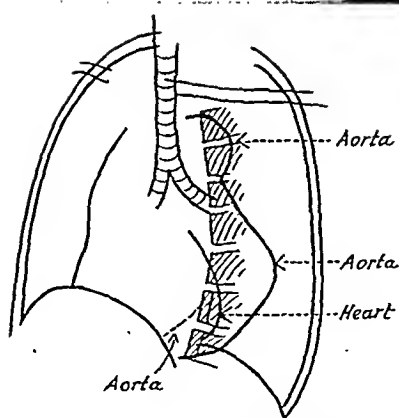


Figure 8—Roentgenogram, left anterior oblique view. Case 4.

not be visualized, dilatation cannot be excluded, but clinically and serologically no evidence of luetic aortitis or aneurysm was present.

CASE 4.—The fourth case, Baker Memorial, Massachusetts General Hospital, X-ray No. 2176, March 10, 1931, was a woman 50 years old with osteomalacia. There had been a definite history of dietary insufficiency for a period of years. No parathyroid tumor was found. Her symptoms and signs consisted of pain in the back and hips with definite tenderness along the ribs and crests of the ilia with dorsal kyphosis. The Hinton (Wassermann) reaction was negative. The renal function test was normal. The nonprotein nitrogen in the blood was normal in amount, but the blood phosphorus was low. The Graham test was negative.

Physical examination was negative except for the condition of the bones. Her blood pressure was 140 mm. mercury systolic and 85 mm. diastolic. The x-ray finding of the kinked aorta was incidental in the course of routine examination.

The anteroposterior view of the heart shadow by x-ray (Fig. 7) shows moderate cardiac enlargement and a curved, well visualized, descending thoracic aorta which can be seen in its lower portion behind the shadow of the heart. The ascending aorta is tortuous also and the knob is prominent. The heart is moderately enlarged and transverse in position. In the left anterior oblique view (Fig. 8) there is quite clearly visible a kink in the aorta, rather high up, just below the origin of the great thoracic vessels. The aorta can be seen descending to the diaphragm behind the heart shadow.

There is no evidence of lues in this case and coarctation of the aorta can also be excluded.

SUMMARY

Four cases of arteriosclerosis, with or without hypertension or lues, are described in which unusual x-ray findings of the descending aorta were detected. One case showed the vessel situated far out in the right chest. Aneurysm of the ascending aorta had to be considered in the differential diagnosis. Forward displacement of the trachea in this connection constitutes a new observation.

The other three cases showed kinking in the course of the vessel; differential diagnosis of aneurysm of the descending aorta and of coarctation of the aorta had to be considered.

In all four cases the use of oblique views was of the greatest value. Abnormal lengthening of the aorta due to sclerosis and hypertension explains these findings.

We are indebted to the X-ray Department of the Massachusetts General Hospital, Dr. George W. Holmes, Director, for cordial assistance in studying these cases, and to Dr. Arlie V. Boek for permission to record his patient, Case 4.

THE SUBCLAVIAN PULSE IN AORTIC VALVE DISEASE*†

HAROLD FEIL, M.D.

CLEVELAND, OHIO

DEFORMITY of the aortic orifice has long been known to alter the character of the arterial pulse. These variations from the normal were first studied clinically by palpation, later by the various types of mechanical sphygmographs, and recently by optical registration. The radial pulse has been carefully studied by clinical and instrumental methods and the results correlated.^{1, 2} The subclavian pulse is a more desirable source of instrumental registration because of its large size and its nearness to the aorta. In addition the subclavian pulse contour is similar to that of the aortic pulse and is relatively free from changes in transmission. Optical registration permits not only the accurate study of contour changes but also the study of the dynamics of the heart in various valve lesions. In this way the findings in experimentally produced valve lesions may be correlated with the records of clinical cases. The clinical pulse in free aortic insufficiency may be distinguished from the pulse modified by varying degrees of stenosis. The records permit the study of the finer details of pulse contour and serve as an accurate check of clinical examination. In aortic insufficiency the water-hammer and collapsing features may be carefully analyzed.

Pure aortic insufficiency induced experimentally³ in dogs produces a central (aortic) pulse curve of characteristic contour. The anacrotic rise is steep, and systolic vibrations are often superimposed on the top of the curve, while the incisura is sharp and deep. The after vibrations are slight or lacking and the diastolic decline is rapid. Likewise the central pulse curves of experimental aortic stenosis⁴ are of characteristic contour. The initial rise which is abrupt and is low on the anacrotic rise is followed by an incisura. The curve then rises slowly to its summit at the end of ejection with vibrations interrupting the rise. From experimental data one anticipates in free aortic insufficiency in man the following pulse characteristics: A large pulse with an interrupted rapid ascent cut by vibrations near the summit; the incisura deep and after vibrations slight or lacking; and a rapid diastolic decline. Likewise in clinical pulse curves of patients with aortic insufficiency modified by moderate stenosis some evidence of an

*From the Medical Clinic of Western Reserve University at City Hospital and the Cardiac Clinic of Mt. Sinai Hospital, Cleveland.

†A brief report of this work was given at the meeting of the Central Society for Clinical Research, November 22, 1929.

anacrotic incisura should be found which is not displayed by the curves of uncomplicated aortic insufficiency while the incisura and diastolic fall should be less precipitous.

CLINICAL CASES

Ninety-four patients with accepted evidence of aortic valve deformity were studied, and in twenty-two instances pathological examinations were subsequently made. These cases were easily divided clinically into three groups: (1) those with evidence of free insufficiency (caused by syphilitic valvulitis and by acute and subacute bacterial endocarditis), thirty-five cases; (2) those with less free insufficiency and modified by varying degrees of stenosis (caused by healed rheumatic scars), forty-four cases; (3) those with frank signs of aortic stenosis (caused by rheumatic and arteriosclerotic scarring), fifteen cases. The central (subclavian) pulses in these clinical types were studied by optical

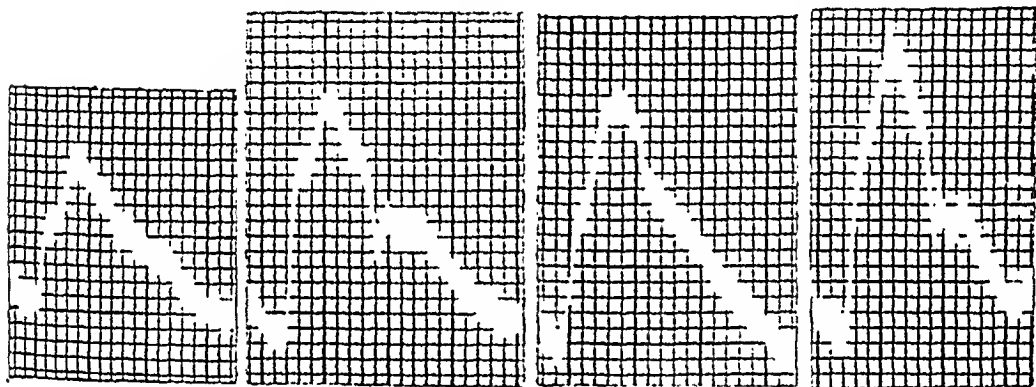


Fig. 1.—Normal subclavian pulse curves.

registration, and comparisons were made between the records and the clinical data.

Post-mortem examinations were made on twenty-two of the patients: (a) in six cases of rheumatic aortic insufficiency; (b) in fourteen cases of infective aortic insufficiency; (c) in one case of aortic stenosis; and (d) in one case of subacute bacterial endocarditis with aortic insufficiency.

METHOD

Records were taken with a cup receiver firmly placed above the middle of the clavicle, the patient lying in the semirecumbent position. The Wigger's capsule was employed to inscribe the pressure changes photographically, with the electrocardiogram (Lead II). The curves were then enlarged uniformly and studied with regard to contour. In all instances immediate clinical observations of the subclavian pulsation were made by digital palpation. Notes were taken at the time of the registration and comparisons of the clinical data with the sphygmograms were made.

Representative normal records are illustrated in Fig. 1. The steep upstroke is caused by the ejection of blood into the aorta. This initial rapid rise completes from one-half to two-thirds of the anaerotic* and is followed by a more gradual rise to the top of the pulse. This summit may be sharp or rounded and is succeeded by a short and steep fall. Ejection terminates at the beginning of the incisura when ventricular diastole begins and there occurs a reverse movement of the blood column toward the aortic valves as they close. Following the incisura are several after vibrations which are simultaneous with the second sound. The curve then falls away gradually in diastole, broken in its descent by slight vibrations, due to the reflection of the pulse wave by the branching arterial tree.

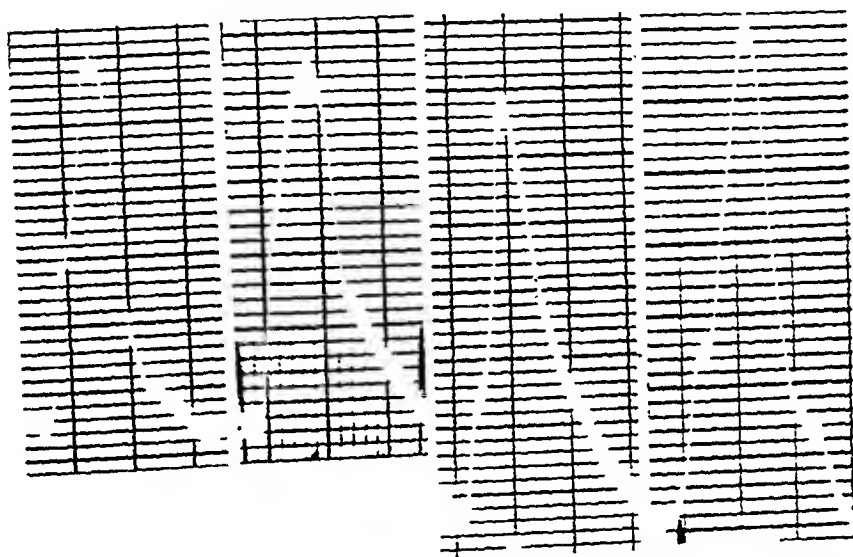


Fig. 2.—Subclavian curves from patients with aortic regurgitation caused by syphilis.

1. *Pure Aortic Insufficiency.*—Records were taken from patients with unmistakable clinical signs of free aortic insufficiency. Clinically, the radial pulse was large and typically Corrigan in quality. The rise was steep, the pulse top sharp and ill-sustained, and the fall rapid. The subclavian pulse was similar in its characteristics. Pulses like these were found most frequently in aortic insufficiency due to syphilitic pathological change and in acute and subacute bacterial endocarditis.

The recorded pulses (Fig. 2) show a sudden steep initial rise hesitating one-fourth to one-half the total height of the anaerotic.† The rise succeeding this interruption is almost equally rapid and terminates in a sharp peak, followed by a rapid cataerotic. Rarely are vibrations seen on the top of the inscribed records. The anaerotic

*As pointed out by Wiggers, the normal subclavian pulse frequently has this anaerotic interruption.

†Analysis of the curves shows that ejection causes this initial rise (not the pressure increase during the brief isometric period).

interruption is found lower down on the ascent than on either normal curves or on those of rheumatic aortic insufficiency. The bottom of the incisura is found after 0.7 of the catacrotns has been inscribed (in normals this figure was 0.3-0.5). The incisura thus is deeper and there is little evidence of an after vibration. These curves are characteristic, and in fourteen instances the diagnosis of luetic aortic disease was confirmed by autopsy. The lesion of syphilis as described

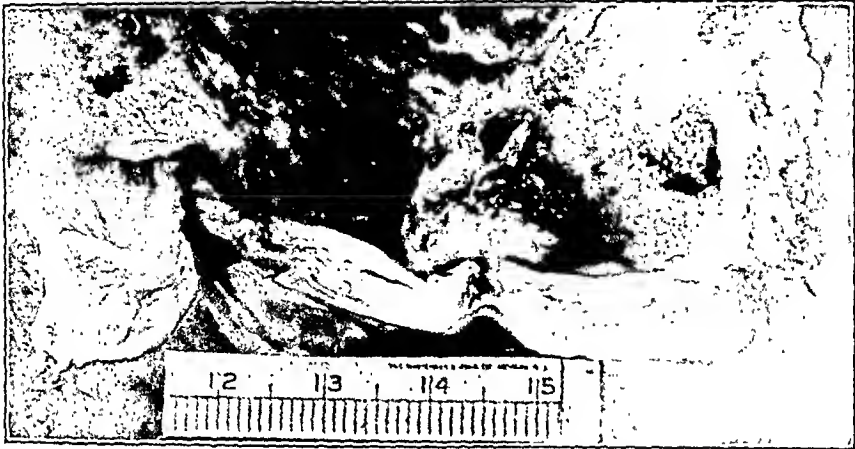


Fig. 3.—Aortic valve distorted by syphilitic changes.

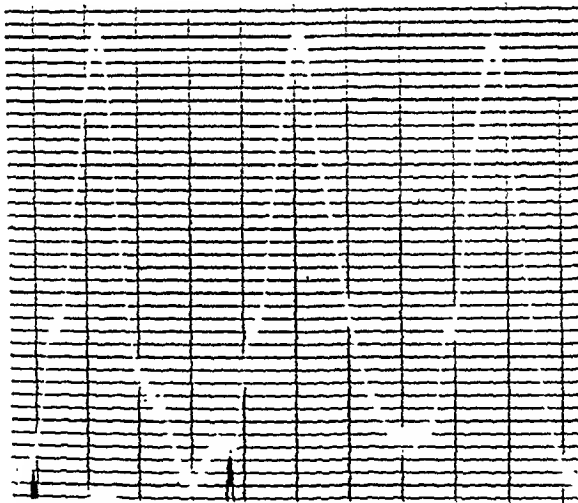


Fig. 4.—Subclavian pulse curve from patient whose aortic valve is illustrated in Fig. 3.

by Scott⁵ begins in the aorta and involves the aortic leaflets first at the commissures. Later, the commissures are widened, the leaflets are deformed, and the ring is dilated. The pathological process results in relatively pure insufficiency of the valve, and the ejection of blood from the left ventricle is free and unobstructed. It is interesting to note that the pulse records differ from those obtained by Wiggers³ in animals with experimental aortic insufficiency in that the experimental curves do not show the anacrotic interruption low on the ascent, but otherwise are similar. Fig. 3 shows the aortic valve of a patient who

had clinical evidence of free aortic regurgitation. The subclavian pulse was large and the summit was rapidly reached. The top of the pulse was poorly sustained and the catacrotus fell away rapidly. Dilatation of the ring, rolling of the leaflets, and separation of the leaflets is seen in the photograph. Fig. 4 is the subclavian pulse curve recorded from this patient and illustrates graphically the examiner's sensations.

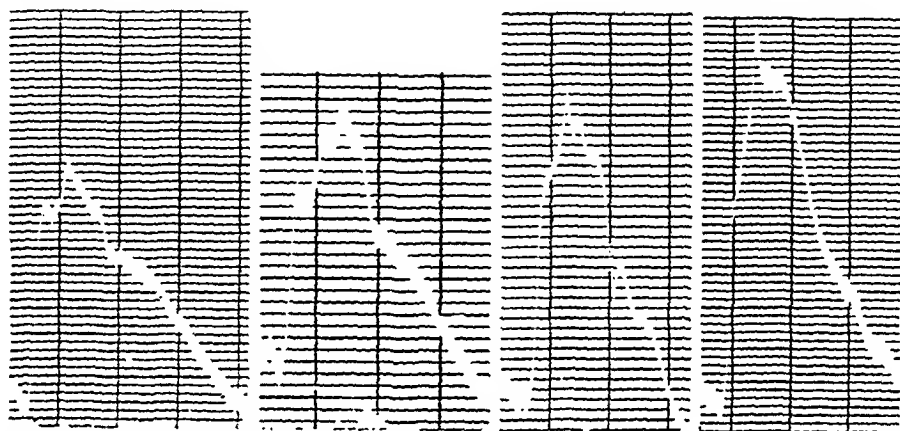


Fig. 5.—Subclavian curves from patients with aortic regurgitation caused by rheumatic process.

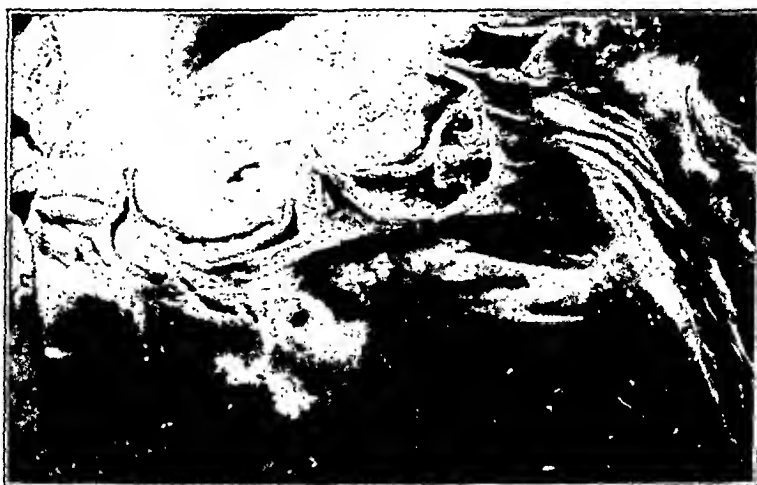


Fig. 6.—Aortic valve distorted by rheumatic changes.

2. *Curves of Aortic Insufficiency With Some Evidence of Stenosis.*—Curves were taken from young patients with a history of rheumatic fever and who had no evidence of syphilis. Clinically the subclavian pulses were Corrigan in quality and were felt to rise steeply and reached the summit near the end of the pulsation. At the top of the pulse which was sustained, vibrations were felt. The diastolic fall did not seem abnormally rapid or deep. These clinical impressions were confirmed by the graphic records (Fig. 5). The rapid rise is occasionally interrupted by a notch two-thirds the distance up the

ascent. The pulse continues to rise after the first steep ascent and the top of the pulse, which is usually cut by vibrations, is reached near the end of ejection. The drop to the incisura is steep but does not extend much farther than the normal and the diastolic portion of the curve falls away gradually. Following the incisura are slight after vibrations, lacking in some curves. These records are strikingly like experimental curves of this valve lesion. Post-mortem studies in rheumatic aortic insufficiency usually reveal varying degrees of stenosis. The aortic ring generally is not dilated and the leaflets are stiffened in their partially diastolic position. In addition they are adherent at their commissures. This is illustrated in Fig. 6 showing the aortic orifice of a patient aged twenty-one years with a rheumatic history and clinical signs of free insufficiency. The subclavian pulse was large, rose steeply, and was fairly well sustained. The graphic pulse curve (Fig. 7) showed the characteristics just described.



Fig. 7.—Subclavian pulse curve from patient whose aortic valve is illustrated in Fig. 6.

3. *Aortic Stenosis*.—Patients presenting the accepted clinical signs of advanced aortic stenosis were studied. The diagnostic criteria were as follows: Small volume pulses, anaerotic in quality, palpable systolic thrill and harsh systolic murmur over the aortic area, transmitted to the neck vessels; either a faint second sound was heard or a slight diastolic murmur. These patients all had subclavian pulses that were reduced in volume, slow in ascent, with the rise definitely interrupted by palpable vibrations. The patients had either rheumatic or arteriosclerotic scarring of the aortic orifice. The graphic records (Fig. 8) illustrate these sensations accurately and in addition show other features. The first rise is abrupt but brief and is terminated by a sharp peak. This is followed by an incisura. The succeeding rise is slow, is cut by vibrations, and ends in the summit of the pulse. The drop to the incisura is usually reached in 0.3 to 0.5 of the total fall, depending on the degree of the associated insufficiency, the wave then

falling away gradually in diastole. These clinical records may be compared with curves obtained in animals with experimental aortic stenosis⁴ and exhibit striking similarity. The small amplitude of the pulse curve with a sharp initial rise, an anaerotic incisura relatively low on the upstroke, a slow ascent cut by vibrations, the rounded summit, the indefinite cataerotic incisura and gradual fall in diastole duplicate the picture found in the experimental curves.

Modifying changes in cardiodynamics in patients with aortic insufficiency produce curves preserving the general contour yet showing some variations:

1. Advanced failure. The pulse curves obtained from patients having the usual clinical evidence of aortic insufficiency and in addition signs of congestive failure presented a small pulse, Corrigan in quality. The subclavian curve showed the sudden and sharp anaeroticus terminating in a sharp and ill-sustained peak, with a rapid diastolic

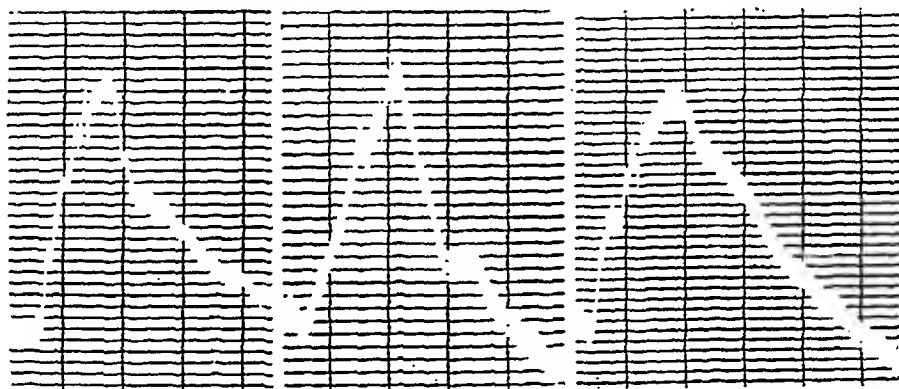


Fig. 8.—Subclavian curves from patients with aortic stenosis.

decline. This pulse although preserving the general contour seen in free insufficiency was reduced in size.

2. Bradycardia. The effect of slow rate was studied in a patient who in addition to free aortic insufficiency of luetic origin had complete heart-block with a ventricular rate of 40. The record showed an abrupt rise terminating in a relatively sharp summit and a rapid fall in diastole. Thus with a prolonged diastole and increased diastolic filling of the ventricle, sudden and rapid ejection took place which led to the conclusion that there could be little or no aortic obstruction. At post-mortem the typical changes of luetic aortitis with involvement of the aortic leaflets were found—the ring being considerably dilated.

3. Tachycardia. Curves with moderate tachycardia in patients with free insufficiency were typical of those found in free insufficiency, and in spite of the increase in rate the diastolic portion of the curves fell away rapidly. Curves recorded in the rheumatic aortic insufficiency group likewise were similar to those with slower rates.

DISCUSSION

Aortic Insufficiency.—Aortic regurgitation of luetic origin is comparable with the insufficiency experimentally produced because both lesions are relatively pure. The central pulse curves in the two while bearing considerable resemblance to one another are not identical in contour. The initial rise, in the clinical cases, terminating in an incisura, is due to the wide open orifice permitting the effective intra-ventricular pressure to be almost immediately transmitted to the aorta because the aorta and the left ventricle are in effect one chamber.* In clinical cases the aortic orifice is in addition dilated and often widely so. The aorta and large peripheral arteries are dilated, and this factor is an additional cause of the low diastolic pressure and reduced peripheral resistance. The experimental lesion produces an insufficient valve and may produce some dilatation of the aortic ring, but is not associated with the dilated peripheral arteries. The clinical curves in pure insufficiency show an anacrotic interruption low on the ascent while the experimental lesion produces curves rising steeply without this hesitation or notch.

What is the explanation for this difference in pulse contour? In the clinical curves the first part of ejection meets with little peripheral resistance, hence the sudden rise of the pulse curves. The hesitation or notch may represent the resistance caused by initial aortic filling. The subsequent rise of the pulse, while steep, is slower, due to the greater peripheral resistance offered by a partly filled aorta. The vibrations on the top of the experimental curves may be due to the vibrations of the aorta initiated by the sudden ejection of an augmented ventricular contents. These vibrations are slight or lacking in the clinical curves because of the damping effect of the dilated arteries.

The interruption in the anacrotic portion of the curve found low down on the curves of free insufficiency is lacking or is found higher up on the curves of rheumatic aortic insufficiency. These curves resemble more closely in their first portions the curves of experimental lesions. This concordance is due to the fact that the aortic ring is less dilated and in this more nearly approximates the experimental lesion. The catacrotic portion of the curves in clinical cases falls more steeply in pure insufficiency than in insufficiency modified by stenosis. Likewise the diastolic portion of the curve falls away more rapidly—both factors due no doubt to the freer ejection and the larger leak.

Aortic Stenosis.—The curves of aortic stenosis in clinical and experimental lesions resemble one another, although the almost constant

*Katz and Felt² showed that the isometric period is distinctly shortened in clinical cases of aortic regurgitation.

presence of some insufficiency in the clinical cases makes the two lesions not precisely comparable. The predominance of the stenotic lesion masks in a great measure the effect of the insufficiency in the clinical cases. This result of insufficiency is best seen in the cataerotic portion of the clinical curves—both in the fall in pressure during reduced ejection and in the diastolic portion of the curves.

SUMMARY

The subelavian pulse was studied in ninety-four patients with aortic valve disease. The curves of aortic insufficiency may be divided into two groups: (a) pure insufficiency, as caused by lues and by bac-

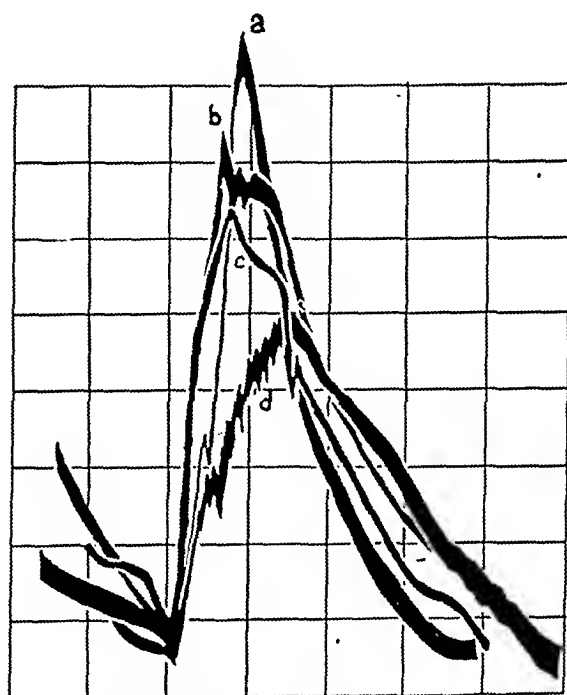


Fig. 9.—Superimposed subelavian curves in various types of aortic valve disease and normal control. See text.

terial endocarditis. These curves have been described and differ in some details from the experimental curves; (b) curves with some evidence of stenosis, found clinically usually in rheumatic cases. These curves more nearly resemble the experimental curves, especially in the anaerotic portions. The records of aortic stenosis are characteristic. Because they give evidence of the freedom of the insufficiency and the degree of the stenosis, subelavian pulse curves have diagnostic value in the differentiation of pure insufficiency from insufficiency modified by stenosis and in cases of aortic stenosis. Fig. 9 illustrates the various types of subelavian curves recorded in aortic valve deformity. The curves, traced from clinical records, are superimposed. Curve *c* is the normal control; *a* is from a case of free insufficiency of

lucetic origin; *b* is from a case of aortic insufficiency with slight stenosis (rheumatic etiology); and *d* is a curve of stenosis. These records illustrate in a comparative way the various types.

REFERENCES

1. Feil, H., and Gilder, M. D. D.: *Heart* 8: 4, 1921.
2. Feil, H., and Katz, L. N.: *AM. HEART J.* 2: 12, 1926.
3. Wiggers, C. J.: In press.
4. Katz, L. N., Ralli, E. P., and Cheer, S. M.: *J. Clin. Investigation* 5: 205, 1928.
5. Scott, R. W.: *Arch. Int. Med.* 34: 645, 1924.
6. Katz, L. N., and Feil, H. S.: *Heart* 12: 171, 1925.

DIGITALIS DOSAGE IN AURICULAR FIBRILLATION

THE INFLUENCE OF THE ACTIVITY OF THE CARDIAC NERVES ON THE SIZE OF THE EFFECTIVE DOSE*

ERNST P. BOAS, M.D.

NEW YORK, N. Y.

DIGITALIS has been in common use for about a century and a half, and it would seem that after so many years little that is new could be added to our knowledge of its method of employ. Yet, as can be attested by every physician who sees a large number of patients with heart disease, many of the sick suffer needlessly and even die because they have received improper treatment with digitalis. In large part, of course, this is due to lack of application of existing knowledge, for Withering himself pointed out that enough of the drug must be given to produce a definite action, such as slowing of the pulse, diuresis, or vomiting.

In recent years, particularly in the United States, much attention has been directed to the standardization of digitalis preparations, and to the establishment of doses adjusted to the body weight of the patient, and to the speed of excretion of the drug. These studies have been valuable in improving the available preparations of digitalis, in encouraging more adequate dosage, and, in particular, in making possible quantitative investigations of digitalis administration. On the other hand, they have unfortunately led to a too rigid routine in the employment of the drug, and to a too implicit reliance on the dose as theoretically worked out, with a corresponding neglect of the clinical criteria of digitalis action. This schematization has arisen in spite of the fact that Eggleston in his original paper¹ reported that in 17 of 48 cases, doses of digitalis much larger than the average were given without the production of more than mild toxic symptoms. Mackenzie and many German observers have repeatedly emphasized the differences in susceptibility of individuals to digitalis. No adequate explanation has been offered for these varying degrees of tolerance to the drug.

In a previous communication² I again drew attention to the lability of the ventricular rate in patients with auricular fibrillation who were under the influence of digitalis, and pointed out that alterations in rate are governed by neurogenically determined changes in conductivity of the specific conducting tissue of the heart. The ventricular rate in these patients is therefore largely controlled by the cardiac

*From the medical service, (Dr. George Baehr) Mt. Sinai Hospital, New York.

nerves. It was further shown that patients with auricular fibrillation and labile ventricular rates, are, as a rule, high strung and nervous, corresponding to patients with neurocirculatory asthenia, and that in them, quantities of digitalis in excess of the calculated body-weight dose are required to slow the ventricles. In patients with auricular

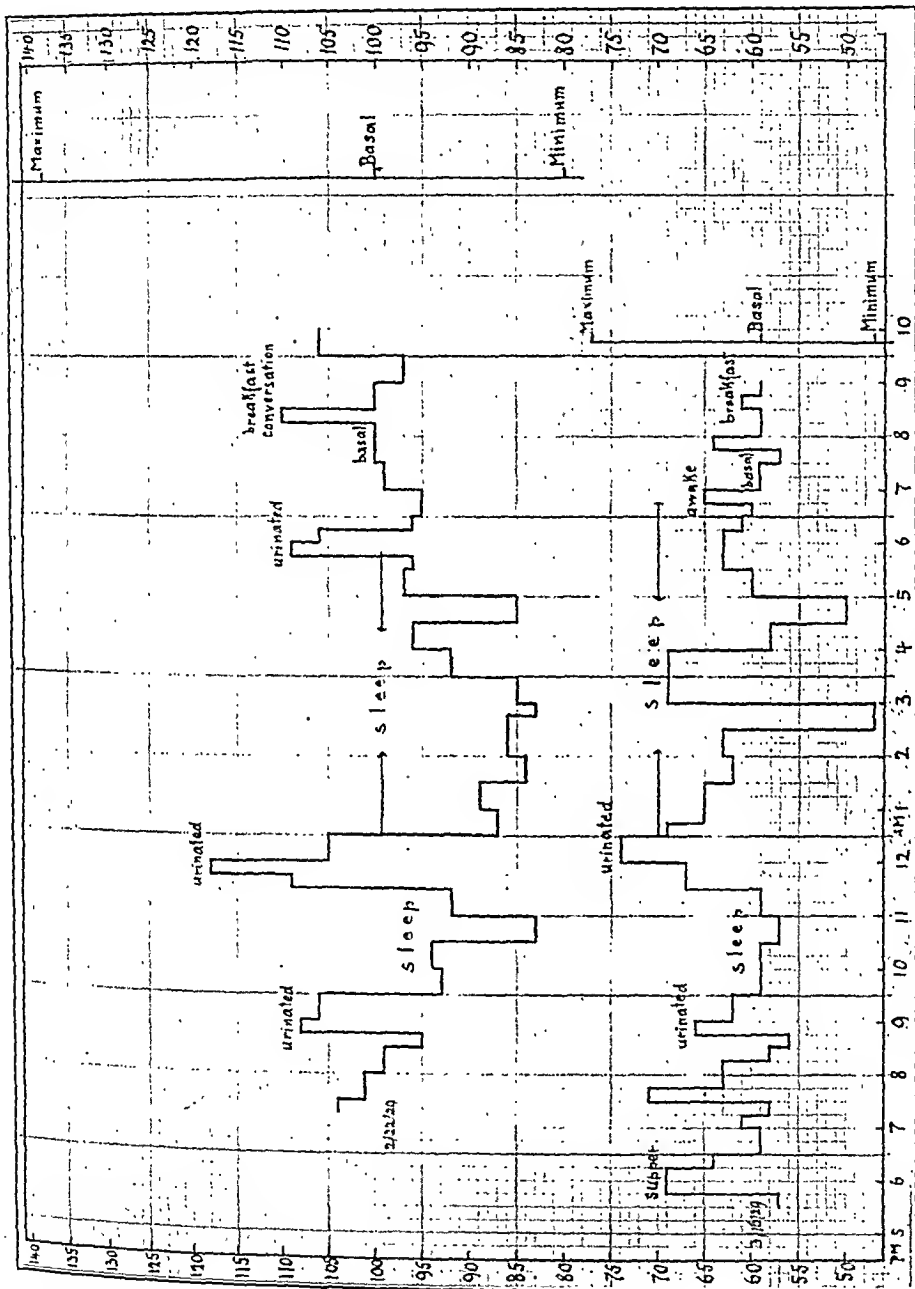


Fig. 1.—Heart rate in a phlegmatic individual with rheumatic mitral stenosis. Upper curve—undigitalized. Lower curve 36 c.c. tincture of digitalis in the preceding thirteen days.

fibrillation and a more stable ventricular rate the usual and smaller dosage with digitalis is efficacious in controlling the ventricular rate. It was pointed out that the dosage of digitalis necessary to achieve a certain effect depends as much on the vagus-accelerator balance as upon the body weight of the patient, and that patients with different nervous constitutions react differently to identical doses of digitalis when their auricles are fibrillating. Patients with increased acceler-

In addition she had a left hemiplegia of embolic origin of two years' duration. The upper record was taken at a time when she had received no digitalis for five months; the ventricular rate was not very rapid. The second tracing taken after 36 c.c. of the tincture of digitalis had been administered in the preceding thirteen days shows very adequate slowing of the ventricles.

In contrast to this case is the one represented in Fig. 2. This was a woman aged forty-six years who also had rheumatic mitral stenosis and insufficiency, and marked generalized cardiac enlargement, and auricular fibrillation. Her lungs were clear, and there was no edema, but the liver extended four fingers below the costal margin. During the first observation, although she had received 51 c.c. of the tincture of digitalis in the preceding twelve days, that is more than 4 c.c. a day, her ventricular rate was still labile and rapid. It was only after 44 c.c. more were given in the succeeding ten days that the ventricular rate was adequately slowed and stable. The patient was a very nervous excitable woman corresponding to the type exhibiting neurocirculatory asthenia.

Age.—Few accurate data are available regarding the influence of the age of the subject on the size of the effective dose of digitalis. McCulloch and Rupe,³ studying children with normal hearts, found great variations in the dose necessary to produce a digitalis response. As criteria of digitalis action they used the appearance of sinus arrhythmia, slowing of the pulse, vomiting, or changes in the P-R interval and in the T-wave. They found that, as a rule, children required body-weight doses two to five times as great as those determined by Eggleston for adults. Jacobsen and Davison,⁴ studying children with congestive heart failure, estimated the dosage for children as about twice that of adults. Schwartz and Weiss,⁵ after administering a single full body-weight dose to each of 23 children, did not observe any toxic manifestations such as nausea or vomiting. In two children with auricular fibrillation adequate slowing of the ventricles resulted within twenty-four hours. Dr. May Wilson informs me that, in her experience, children require larger doses of digitalis relative to their body weights than do adults. On the other hand, Sutton and Wyckoff,⁶ report that in children digitalis is effective in doses comparable to those required by adults, without necessarily producing intoxication.

In the elderly the pulse tends to be slow, and small doses of digitalis slow the ventricles in the presence of auricular fibrillation. Such a case is illustrated in Fig. 3, a record of the ventricular rate of a man of seventy years with auricular fibrillation who had a heart of normal size and shape, with no valvular disease, and a blood pressure of 120/65 mm. He exhibited a slow ventricular rate although he had received no digitalis. That this slow rate was not conditioned by an organic lesion of the conducting tissues is proved by the fact that

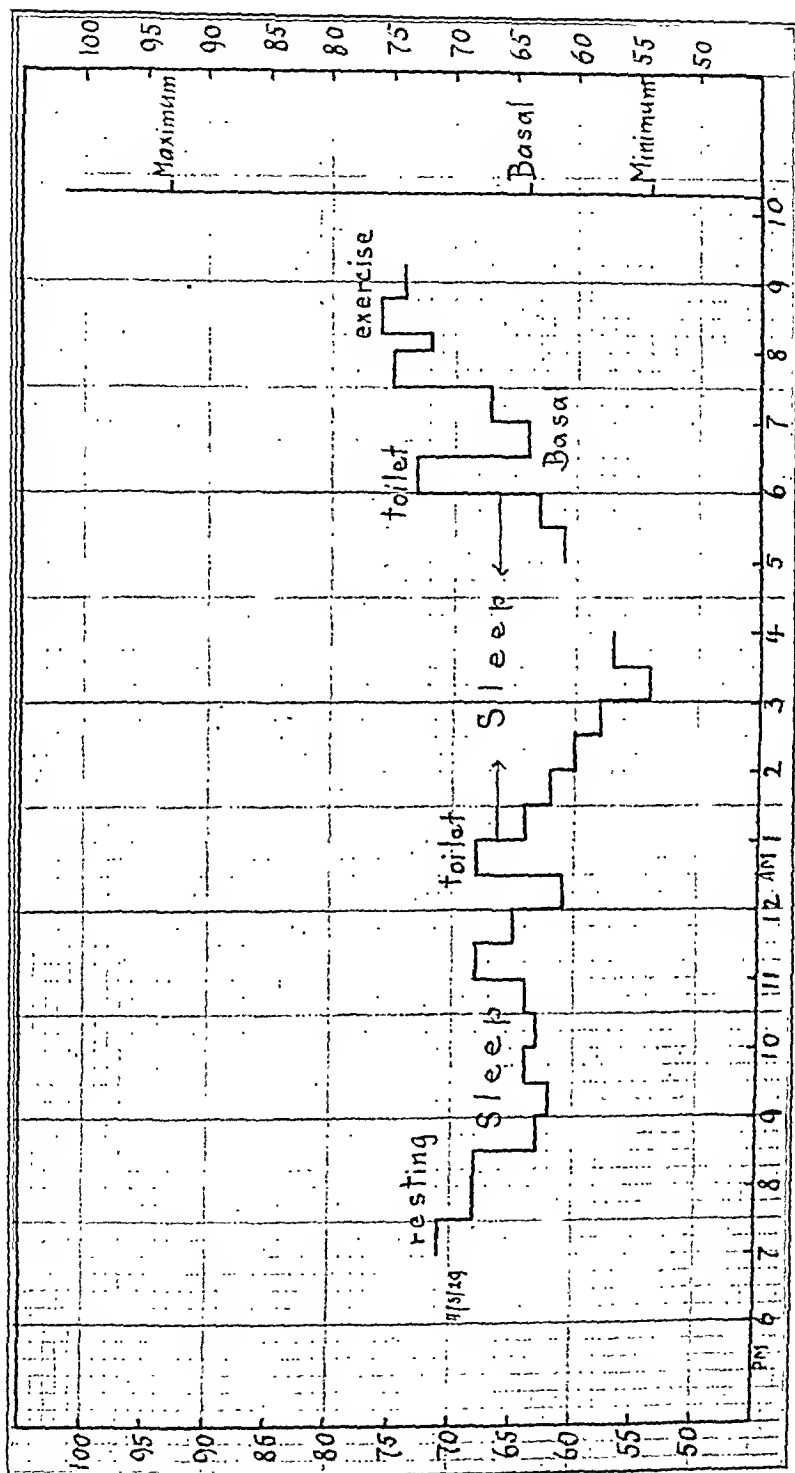


FIG. 3.—Heart rate in a man of seventy years, with arteriosclerosis. Undigitalized.

four weeks later he had normal sinus rhythm, and the electrocardiogram showed no delay in conduction.

On the other hand, it is well known that organic lesions of the conducting tissue, which occur particularly in older individuals, lead to slow ventricular rates in the presence of auricular fibrillation. Such a case is represented by R. L., a man aged sixty-seven years who had auricular fibrillation with a heart of normal size, without valvular lesions, and with a blood pressure of 140/70 mm. There was marked general arteriosclerosis. Under 3 c.c. of tincture of digitalis a day his heart rate ranged from 50 to 60. Sinus rhythm was restored with quinidine, and the heart rate remained unchanged. The P-R interval measured 0.25 seconds. Five days later auricular fibrillation again set in, and now free from the influence of digitalis the ventricular rate was 60 to 80.

Although exact experimental data are not available, it seems clear that, in general, in children, vagus activity is not marked, and sympathetic activity predominates; whereas with increasing age there is a shift in the balance of vagus and sympathetic to the side of increased vagus influence.⁷ This phenomenon, in so far as it improves intracardiac conduction in children, and slows it in the elderly, helps explain the more labile ventricular rates in children and the more stable rates in the aged. It also makes understandable the fact that, as a rule, children must receive larger doses of digitalis than elderly individuals to control the ventricular rate when the auricles are fibrillating.

Fever.—The ineffectiveness of digitalis in slowing the pulse during fevers has long been noted, so that many clinicians do not use the drug when there is fever. Here we are concerned only with the effect of febrile states on hearts with auricular fibrillation, not with sinus rhythm. A diminished vagus, or increased accelerator activity, or both are operative in febrile states.^{8, 9} Cohn and Jamieson,¹⁰ found accelerated conduction from auricles to ventricles in 11 of 50 patients with lobar pneumonia. In the presence of auricular fibrillation this improved conduction leads to a rapid ventricular rate. Schwartz and Weiss,⁵ were unable to slow the ventricles in children with active rheumatic fever and auricular fibrillation, with body-weight doses of digitalis, although in these same children the usual doses were effective when the infection had subsided.

In my experience patients with fever often tolerate much larger doses of digitalis than do normal individuals, and very large doses must be given to slow the ventricles when the auricles are fibrillating.¹¹ That such slowing can be achieved is illustrated by the following example:

A woman aged 45 years who had had mitral stenosis and auricular fibrillation for some time was admitted to Mt. Sinai Hospital with lobar pneumonia. When first seen she was intensely cyanotic and dyspneic, with a ventricular rate of about

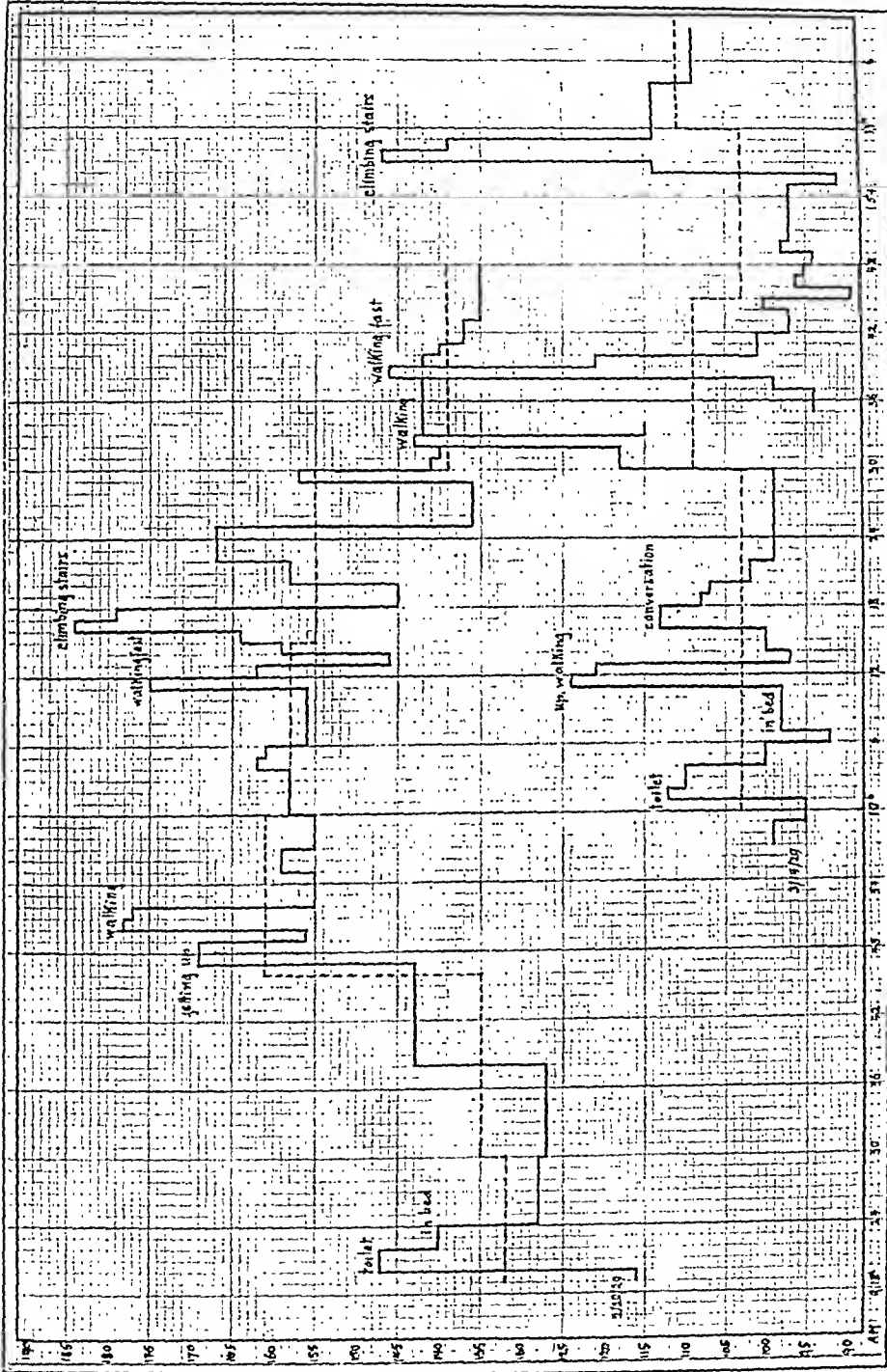


Fig. 4.—Unstable ventricular rate in a woman with Graves' disease. Upper curve—undigitalized. Lower curve—digitalized. curve after 61 c.c. tincture of digitalis in the preceding sixteen days.

150, respirations of 36, and temperature 103° F. She received 19 c.c. of the tincture of digitalis within the first twenty-four hours. Within fifteen hours her ventricular rate was 112, and at the end of twenty-four hours it was 97. She then received about 2 c.c. of the tincture daily, and during the following week while her temperature ranged from 101° to 102° , her ventricular rate remained between 60 and 70. With this there was very pronounced improvement in her condition.

This case shows that an adequate digitalis effect can be obtained in patients with auricular fibrillation and intercurrent febrile episodes, if sufficiently large doses are administered.

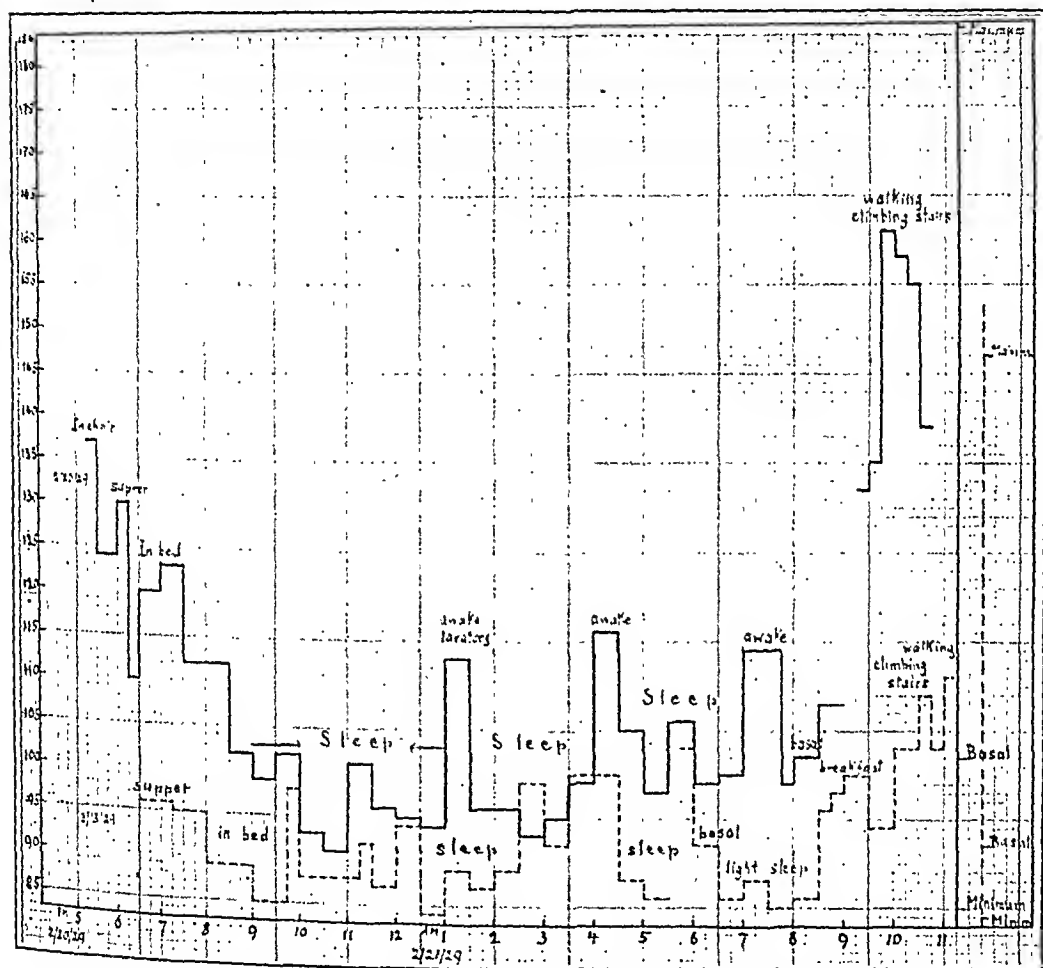


Fig. 5.—Heart rate in the same patient. Solid lines—undigitalized. Broken lines after 61 c.c. tincture of digitalis in the preceding sixteen days.

Graves' Disease.—In Graves' disease, as in fevers, the experience of clinicians has been that digitalis is ineffectual in slowing the heart rate, whether there be sinus rhythm or auricular fibrillation. Wenckebach states that patients with auricular fibrillation and Graves' disease do not react well to digitalis.¹² It has been my experience that patients with Graves' disease and auricular fibrillation, exhibit rapid ventricular rates, and that the ventricles react to all reflex stimuli by excessive acceleration. Very large doses of digitalis are required to slow the ventricular rate, and even after adequate slowing the ven-

tricles respond intemperately to reflex stimulation. These large doses can be tolerated without toxic symptoms. The following case offers a good illustration:

A woman aged 50 years was admitted to the Mt. Sinai Hospital Dispensary with classical signs and symptoms of Graves' disease. Two years previously, following an automobile accident, she had begun to lose weight and to tire easily, so that she was unable to do her housework. For six months she had had attacks of palpitation with a sense of suffocation. There was sweating, tremor of the hands and progressive loss in weight. Radium therapy had been ineffectual. On admission she exhibited slight exophthalmos, a von Graefe sign, a slightly enlarged thyroid isthmus, marked tremor of the hands. The heart showed considerable enlargement of the left ventricle, and auricular fibrillation. The basal metabolic rate was +65. Her heart rate was recorded by means of the cardiotaehometer. Fig. 4 shows the ventricular rate recorded every few minutes both before and after digitalization. The excessive accelerations following moderate exertion are striking, even after she had received large doses of digitalis. In Fig. 5 is recorded the heart rate for two periods of about seventeen hours each, once before digitalis had been given, and after 61 c.c. of the drug had been given in sixteen days. There were no symptoms of digitalis intoxication, the rate during sleep did not go below 85, and a maximum of 147 was reached after exercise.

At times the increased tolerance to digitalis of a patient with Graves' disease may be of diagnostic value. This is well illustrated by the following case.

W. A., (hospital No. 325061) a man aged 60 years had had increasing weakness, dyspnea on exertion and palpitation for two years. For one month the symptoms had been worse. His weight one year ago was 195 pounds, his present weight 155 pounds. He was a serene, well built elderly man. The eyes were not prominent. The thyroid gland was not palpable, and there was no substernal struma visible on the roentgen film. The lungs were moderately emphysematous, with some râles at the right base. The heart was not enlarged, the sounds were rather faint, and there were no murmurs. The rhythm was absolutely irregular, with a ventricular rate of 150. The electrocardiogram showed auricular fibrillation. The blood pressure was 140/80 mm. There was considerable sclerosis of the radial and temporal arteries. The Wassermann reaction was negative. It was thought that the patient had auricular fibrillation associated with arteriosclerosis. There was no other evident etiological factor. Digitalis was administered. Twenty-one c.c. of the tincture were given in three days, yet the ventricular rate was 120. In the first nine days of treatment 46 c.c. of the tincture were administered; there was no nausea or bigeminy and the ventricular rate did not fall below 90. In the subsequent seven days 39 c.c. more of tincture of digitalis were given with no further drop in pulse rate. The unexplained resistance to the effects of digitalis led to the estimation of the patient's basal metabolism. This was found to be +54 on one occasion and +65 on another.

This case of atypical hyperthyroidism was discovered only because of the exceptionally high tolerance for digitalis.

When the Graves' disease is no longer active, this increased tolerance for digitalis is lost. Thus Fig. 6 represents the ventricular rate of a woman of fifty years who had developed Graves' disease six years

previously. Four years previously she had an enlarged heart with auricular fibrillation, and cardiac failure. The activity of the Graves' disease gradually receded and the cardiac signs and symptoms domi-

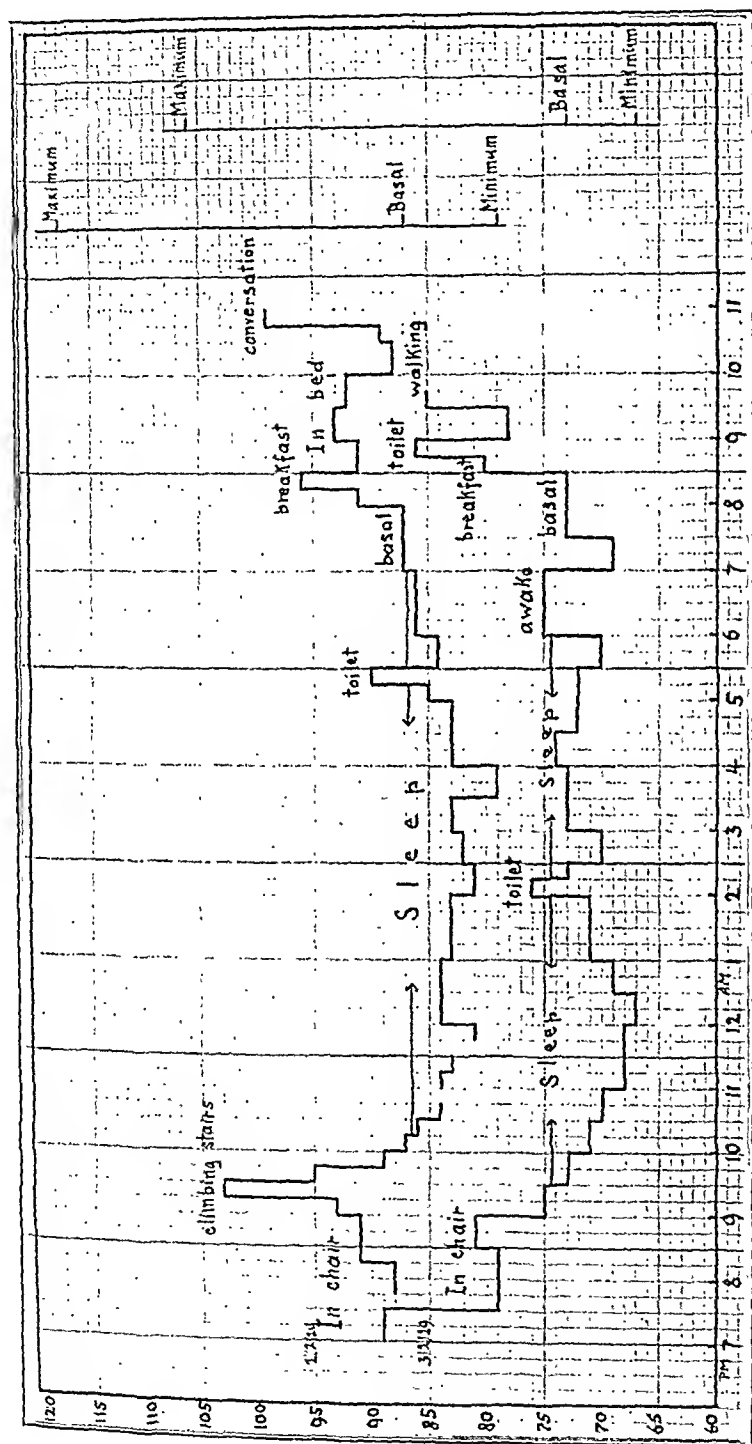


Fig. 6.—Heart rate in a woman with inactive Graves' disease. Upper curve after 17 c.c. tincture of digitalis from Jan. 19 to Feb. 2, 1929. Lower curve, after 23 c.c. tincture of digitalis from Feb. 13 to March 2, 1929.

nated the clinical picture. When the present record was taken the Graves' disease was inactive, the heart showed enlargement of all chambers, and the liver extended four fingers below the costal margin. Daily doses of from 1 to 2 c.c. of the tincture of digitalis adequately controlled the ventricular rate.

Cardiac Insufficiency.—Acceleration of the heart rate with the onset of cardiac insufficiency, in the presence of normal sinus rhythm, is a commonplace clinical observation. The physiological processes that underlie this quickening of the heart are complex and are not fully understood. Alterations of certain chemical factors, such as the hydrogen-ion concentration, the carbon dioxide and oxygen content of the blood, and the accumulation of lactic acid may play a rôle. Another important mechanism is often overlooked. Bainbridge¹³ showed that a rise of venous pressure, or a sufficient increase of the diastolic distension of the heart, brings about reflex acceleration of the heart, due partly to loss of vagal tone, and partly to an increase of accelerator tone. Such reflexes must often be active in the presence of myocardial insufficiency. Kisch¹⁴ has stressed the diminution of vagus tone and the increase in sympathetic tone in circulatory failure, and has ascribed the increased heart rate to this factor. In addition to the Bainbridge reflex, reflexes arising in the carotid sinus undoubtedly play a rôle.

The same mechanism must prevail in heart failure associated with auricular fibrillation, but here the preponderance of sympathetic activity leads to increased conduction from auricles to ventricles, and so to an increased ventricular rate. So it is that, in the presence of marked cardiac insufficiency, larger doses of digitalis are required to slow the ventricles than when compensation has been restored. Mackenzie,¹⁵ long since, noted this phenomenon, and ascribed it to a diminished irritability of the A-V node as the clinical condition of the patient improved. More recently Gold and DeGraff¹⁶ presented data to show that "the degree of heart failure is an important factor in determining the amounts of digitalis necessary to produce full therapeutic results." Their patients with severe heart failure required much larger doses to slow the ventricles than did these who were ambulant.

Some authors believe that patients with auricular fibrillation differ in their sensitivity to digitalis because of differences in the nature and cause of the underlying heart disease. Thus, the slow ventricular rates observed in elderly patients with auricular fibrillation are ascribed to sclerotic lesions of the conducting system. I have compared cases of auricular fibrillation associated with rheumatic heart disease, hypertension, arteriosclerosis, and Graves' disease, and have found that the etiological agent or the anatomical lesion rarely is the determining influence. Differences in tolerance, when they exist, are best explained by the varying state of vagus-accelerator balance. In Graves' disease it is the increased sympathetic activity, in the elderly with arteriosclerosis, it is, as a rule, the increased vagus influence, so common in the aged, rather than fibrotic lesions of the conducting system that governs the reaction of the heart to digitalis.

DISCUSSION

The data that have been presented seem to allow of the following generalizations. In the absence of organic lesions of the conducting system, the ventricular rate in patients with auricular fibrillation is determined by the vagus-accelerator balance, fast and labile rates being associated with preponderant sympathetic action. In patients in whom sympathetic activity is dominant, larger doses of digitalis are required to slow the ventricles, and these larger doses are tolerated without giving rise to toxic symptoms. In childhood, as well as in patients with neurocirculatory asthenia, fever, Graves' disease, and with severe circulatory failure the activity of the accelerator nerves outweighs that of the vagus, and it is just in these clinical conditions that the largest doses of digitalis must be administered to bring about ventricular slowing.

Certain analogies between the slowing of the heart in response to vagus pressure and to digitalis were pointed out some fifteen years ago by Weil¹⁷ and by Fahrenkamp.¹⁸ The latter showed that in patients with auricular fibrillation and rapid ventricular rates vagus pressure induced no ventricular slowing, and that large doses of digitalis were also without effect; that in those patients in whom ventricular slowing followed doses of 1 to 2 grams of digitalis there was definite slowing following vagus pressure; and that patients who exhibited a marked vagus effect were sensitive to small doses of the drug. These observations have led to the generalization that the effectiveness of digitalis medication in patients with auricular fibrillation in general will parallel the degree of ventricular slowing they exhibit following pressure on the carotid sinus.¹⁹

These phenomena reveal the same mechanism that we have described. Presumably, vagus slowing of the heart is induced with greater difficulty when the sympathetic is overactive, and this is true whether the slowing is brought about by mechanical pressure or by digitalis. The regulation of the heart rate is so complex, and there are so many variables involved, that one cannot expect to find, in every individual case of auricular fibrillation, an exact quantitative relationship between vagus-accelerator balance, ventricular rate, and digitalis susceptibility. Yet there is no doubt that this mechanism is, to a large extent, determining. It is very probable that the variable response to digitalis of hearts with normal sinus rhythm is controlled by the same factors. Cohn²⁰ has shown that with sinus rhythm, in the absence of edema, digitalis reduces the rate principally in hypodynamic unstable hearts.

In the treatment of patients with auricular fibrillation, the lability of the ventricular rate is as significant as its absolute level. The marked lability of the heart rate in many patients with auricular fib-

rillation, even when they are under the influence of digitalis, has been pointed out in a previous communication,² and is well illustrated in some of the graphs of the present paper. This variability is evidenced to a much greater degree by individuals with preponderant sympathetic activity. In them, more especially, quantities of digitalis sufficient to produce satisfactory ventricular slowing when they are at rest, are quite inadequate when they are up and about. Very large doses of the drug may be necessary to keep the ventricular rate within

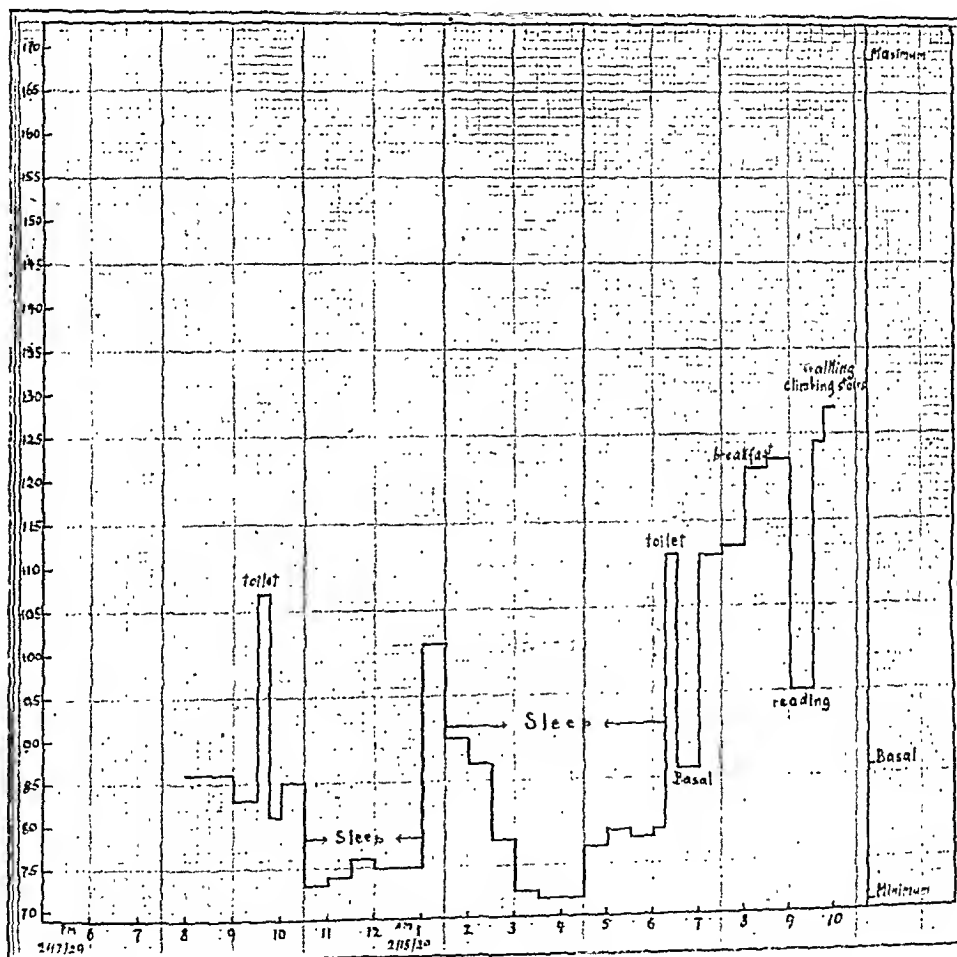


Fig. 7.—Response of ventricular rate in auricular fibrillation to slight exertion.

bounds under such conditions. Fig. 7, representing the ventricular rate of a man with mitral stenosis and auricular fibrillation, shows that although at rest the rate ranges from 75 to 85 a minute, slight exertion, such as eating breakfast, elevates it to 125. To such patients enough digitalis must be given to reduce the ventricular rate at rest to from 50 to 60 a minute, to prevent undue acceleration when they resume their ordinary activities. At times it is impossible to check these unregulated responses of ventricular rate to physical or even emotional activity. For two years I have had under observation a

man with chronic rheumatic valvular disease, mitral stenosis and auricular fibrillation, and a marked anxiety neurosis. He has never had congestive heart failure. The following observations are typical of his reactions to digitalis. Undigitalized, his ventricular rate was about 150. After he had received 52 c.c. of the tincture in ten days the ventricular rate when he was in bed before breakfast was 56. After breakfast it rose to 112; while he was being examined to 120; and after walking across the room to 160. In the following seven days 44 c.c. more of the tincture were given. At the end of this time the rate was 58 at rest, and 80 walking. Because of the development of toxic symptoms, such as headache and anorexia, it has been impossible to keep him adequately digitalized, and he has had repeated courses of quinidine to maintain sinus rhythm, as the only means of keeping him comfortable. It is necessary constantly to reiterate that in the treatment of auricular fibrillation enough digitalis must be given to maintain ventricular slowing when the patient is pursuing his ordinary activities; and that for patients with increased accelerator tone this involves doses much larger than those required to slow the ventricles with the patient at rest.

What practical rules of digitalis dosage may be derived from all of these considerations? The weight of the patient is no absolute guide to the total dose of digitalis that is required. Of equal, if not greater importance is the vagus-accelerator balance. Preponderant accelerator activity manifests itself clinically by a rapid labile ventricular rate, and by many of the signs and symptoms of neurocirculatory asthenia. It is particularly marked in patients with Graves' disease, neurocirculatory asthenia, and severe cardiac insufficiency. It may be anticipated that such patients will require exceptionally large doses of the drug to slow the ventricles in the presence of auricular fibrillation.

In actual practice, when dealing with a patient who has received no digitalis, it is convenient to use the calculated body-weight dose as a rough preliminary guide. One can commence by giving as the first dose, one-half of the theoretical dose which is approximately 0.18 c.c. of the tincture per pound. At the end of six hours 4 c.c. of the tincture are given, and this dose is repeated once after six more hours. Then 2 c.c. are given every six hours until the ventricular rate at rest is about 60. In patients who do not exhibit hyperactivity of the accelerator nerves such dosage very quickly will bring about satisfactory slowing of the ventricles. In those with heightened sympathetic activity this relatively high dosage may have to be continued for many days before the ventricles are controlled. It may be given without fear of toxic manifestations, for these patients rarely show evidences of toxicity before a well-marked slowing of the ventricles occurs. Of

course the patient must be under continuous observation to guard against possible overdosage as manifested by nausea, vomiting, or bigeminy.

Patients with cardiac failure often vomit shortly after taking the drug. This is not a specific digitalis effect, but is probably related to congestion and irritability of the stomach, and is not an indication for suspending further digitalis therapy. In such cases the substitution of the dried leaf for the tincture often enables the patient to retain the drug.

The size of the maintenance dose, once the patient has been digitalized, cannot be predicted, but must be established by actual trial in each case. In general, the greater the original dose that was required to slow the ventricles, the larger will be the maintenance dose. It may range from 1 to 4 or 5 c.c. of the tincture a day. It must serve to control the ventricles when the patient is following his usual mode of life.

All such rules, at best, are but rough guides. Strict individualization and giving enough of the drug to produce the desired effect, irrespective of the size of the dose, are the essence of successful therapy.

SUMMARY

The ventricular rate in patients with auricular fibrillation is largely governed by the balanced activity of the vagus and accelerator nerves. With preponderant vagus activity the rate tends to be slow and stable, with preponderant accelerator activity it tends to be rapid and labile. Patients in whom accelerator influences predominate require much larger doses of digitalis to slow and stabilize the ventricular rate than do those in whom this excess of sympathetic influence is not manifest. This factor of nervous regulation is more potent than the weight of the patient in determining digitalis dosage. The conditions under which auricular fibrillation associated with exaggerated accelerator activity is encountered most frequently in the clinic are: in childhood, in patients with neurocirculatory asthenia, with fever, with Graves' disease, and with severe cardiac insufficiency. In these conditions exceptionally large doses of digitalis must be given to produce and maintain adequate ventricular slowing in the presence of auricular fibrillation.

REFERENCES

1. Eggleston, C.: Digitalis Dosage, *Arch. Int. Med.* 16: 1, 1915.
2. Boas, E. P.: The Ventricular Rate in Auricular Fibrillation, Studies with the Cardiotaehometer, *AM. HEART J.* 4: 499, 1929.
3. McCulloch, H., and Rupe, W. A.: Studies on the Dosage of Digitalis in Children, *Am. J. M. Sc.* 162: 231, 1921.
4. Jacobsen, A. W., and Davison, W. C.: Digitalis Therapy in Cardiac Decomensation in Children, *Am. J. Dis. Child.* 32: 373, 1926.
5. Schwartz, S. P., and Weiss, M. M.: The Effects of Digitalis on the Electrocardiograms of Children with Rheumatic Fever and Chronic Rheumatic Valvular Heart Disease, *Am. J. Dis. Child.* 38: 699, 1929.

6. Suttou, L. P., and Wyckoff, J.: Digitalis, Its Value in the Treatment of Children with Rheumatic Heart Disease, *Am. J. Dis. Child.* 41: 801, 1931.
7. Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, *Arch. Int. Med.* 31: 423, 1923.
8. Rühl, J.: Die Frequenz des Herzschlages, *Handbuch d. Normalen u. Pathologischen Physiol.* Bd. 7, Erste Hälfte p. 515, 1926, Berlin, Julius Springer.
9. Brunton, T. L., and Cash, J. T.: On the Alterations in the Action of Digitalis Produced by Febrile Temperatures, *Practitioner* 33: 272, 1884.
10. Cohn, A. E., and Jamieson, R. A.: The Action of Digitalis in Pneumonia, *J. Exper. Med.* 25: 65, 1917.
11. Bijlsma, U. G., et al: Die Digitalis u. ihre Therapeutische Anwendung, Translated by P. Neukirch, Berlin, 1923, p. 92, Julius Springer.
12. Wenekebach, K. F., and Winterberg, H.: Die Unregelmässige Herztätigkeit, Leipzig, 1927, p. 493, Wilhelm Engelmann.
13. Bainbridge, F. A.: The Influence of Venous Filling on the Rate of the Heart, *J. Physiol.* 50: 65, 1915.
14. Kisch, B.: Beobachtungen bei der Irradiation Autonomer Reflexe im Kreislaufgebiet, *Ztsch. f. Kreislaufforsch.* 23: 241, 1931.
15. Mackenzie, J.: Diseases of the Heart, London, 4 ed., 1925, p. 208, Oxford University Press.
16. Gold, H., and DeGraff, A. C.: Studies on Digitalis in Ambulatory Cardiac Patients. IV. Newer Principles of Digitalis Dosage, *J. A. M. A.* 95: 1237, 1930.
17. Weil, A.: Ergebnisse d. Vagusdruckversuches, *Deutsches Arch. f. klin. Med.* 119: 39, 1916.
18. Fahrenkamp, K.: Klinische und elektrographische Untersuchungen über die Einwirkung d. Digitalis u. d. Strophanthins u. d. insuffiziente Herz, *Deutsches Arch. f. klin. Med.* 120: 11, 1916.
19. Semerau, M.: Die Flimmerarrhythmie, *Ergebn. d. inn. Med. u. Kinderh.* 19: 134, 1921.
20. Cohn, A. E.: Clinical and Electrocardiographic Studies on the Action of Digitalis, *J. A. M. A.* 65: 1527, 1915.

THE EFFECT OF DIGITALIS ON THE T-WAVE OF THE ELECTROCARDIOGRAM. AN EXPERIMENTAL STUDY IN HUMAN BEINGS*

WILLIAM A. BRAMS, M.D., AND PETER GABERMAN, M.D.
CHICAGO, ILL.

FLATTENING or inversion of the T-wave in the electrocardiogram following administration of digitalis has been reported by a number of observers, many of whom regard this change as an early sign of digitalis effect or intoxication (Pardee;^{8, 9} Cohn, Fraser and Jamieson;³ Marvin, Pastor and Carmichael;⁵ Cohn and Stewart⁴). Robinson and Wilson¹⁰ considered such a change in the T-wave as the first evidence of digitalis intoxication. Others found that the T-wave remained upright and became taller after digitalis (Yacoël and Papanayotou;¹² Selenin;¹¹ Nicolai and Simons⁷). There is a general impression in spite of these contradictory reports that inversion or flattening of the T-wave is reliable, early evidence of digitalis effect. McCulloch and Rupe⁶ found inversion of the T-wave in only 11 per cent of children following digitalis administration while about 33 per cent showed changes in rate and conduction.

In a previous publication one of us (W.A.B.²) reported a series of experiments on dogs in which different preparations of digitalis were administered by various routes and in ascending doses until death of the animal occurred. Electrocardiograms were taken three times each day for the duration of the experiment. In not a single instance did the T-wave become inverted in spite of the fact that evidences of digitalis intoxication were present, such as prolonged P-R interval, nodal rhythm, complete dissociation, nausea and vomiting. These results have since been confirmed by Blumenfeldt and Strauss¹ who used rabbits and human patients with cardiac disease, including auricular fibrillation.

It seemed desirable to perform experiments on human beings who had neither a history nor evidence of cardiac disease, since it is possible that persons with healthy hearts react differently from those with cardiac disease. These experiments were conducted like those of the animal series, namely, gradually ascending doses of digitalis were given and electrocardiograms were taken three times each day in order not to overlook early or transient changes—a precaution not taken by some observers who failed to note an inversion of the T-wave.

*From the Medical Department of the Cook County Hospital, Chicago and the Department of Physiology, Northwestern University Medical School.

Nine adult, volunteer patients were selected who were convalescing from peptic ulcer, arthritis and like conditions but who gave no history or evidence of cardiac disease. Digifoline was given once a day intravenously, beginning with 1.0 c.c. and increasing by 1.0 or 2.0 c.c. daily until these ascending doses produced nausea, vomiting and precordial distress. The usual amounts given were 45.0 c.c. in nine days, the patient receiving 24.0 c.c. during the last three days of the experiment. The drug was standardized shortly before use, and it was found that 1.0 c.c. was equal to 1.5 grains of the powdered leaf. Control electrocardiograms were taken before the drug was given and at three, seven and twenty-four hours after each dose. The usual precautions were observed while the electrocardiograms were taken.

Analysis of the electrocardiograms so obtained failed to reveal a single instance of inversion of the T-wave. Nor was there any instance of a previously upright T-wave becoming isoelectric. This was not due to lack of potency or to insufficient dosage of the drug as eight of the nine patients showed a moderate drop in pulse rate, one eventually developed partial heart-block (P-R interval of 0.34 second) and another developed 2:1 heart-block and later, transient auricular fibrillation. All became nauseated and vomited; most complained of a distressing form of precordial oppression.

A slight reduction in amplitude of the T-wave occurred in five cases, the decrease being from 1 to 3 mm. Similar reductions and increases were occasionally seen without other signs of intoxication. There were times when the T-wave decreased slightly after digitalis but would return to the previous level after the next dose which would be larger. In the two patients in whom block developed the T-wave actually increased slightly in amplitude at the time block appeared.

It seems that variations of from 1 to 3 mm. in amplitude of the T-wave should be considered as possibly due to extracardiac causes. The changes in amplitude of T were compared with the corresponding changes in QRS. The two were seldom simultaneously depressed to a proportionate degree. In fact, changes in the opposite direction occurred at times.

The results of our experiments, both on human beings and on animals, lead us to the conclusion that inversion of the T-wave does not always occur, even after toxic doses of digitalis, nor is it always an early sign when it does occur. We cannot regard T-wave inversion as a reliable or early sign of digitalis action. The slight changes in T-wave amplitude might be due to extracardiac factors and position changes of the heart. This should be ruled out before ascribing such changes to digitalis.

SUMMARY

A series of experiments was conducted on persons without history or evidence of heart disease in order to determine the effects of digi-

talis on the T-wave of the electrocardiogram. Ascending doses were given intravenously, daily, until nausea, vomiting, precordial distress and heart-block developed as signs of digitalis excess. In no instance was there an inversion of the T-wave. Minor decrease in the amplitude of T occurred in about one half of the patients but the degree of reduction can be explained on other grounds and an elevation of the same extent occurred at times, viz., when heart-block occurred. Inversion of the T-wave cannot be regarded as an early or constant sign of digitalis effect. This was shown in these experiments in persons without heart disease and in dogs, and similar results have been reported in patients with cardiac disease.

REFERENCES

1. Blumenfeldt, E., and Strauss, S. G.: *Ztschr. f. klin. Med.* 113: 502, 1930.
2. Brams, W. A.: *Arch. Int. Med.* 43: 676, 1929.
3. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: *J. Exper. Med.* 21: 593, 1915.
4. Cohn, A. E., and Stewart, H. J.: *J. Clin. Investigation* 6: 53, 1928.
5. Marvin, H. M., Pastor, R. B., and Carmichael, M.: *Arch. Int. Med.* 35: 782, 1925.
6. McCulloch, H., and Rupe, W. A.: *Am. J. M. Sc.* 162: 231, 1921.
7. Nicolai, G. F., and Simons, A.: *Med. Klin.* 5: 160, 1909.
8. Pardee, H. E. B.: *J. A. M. A.* 75: 1258, 1920.
9. Pardee, H. E. B.: *J. A. M. A.* 81: 186, 1923.
10. Robinson, G. C., and Wilson, F. N.: *J. Pharmacol. & Exper. Therap.* 10: 491, 1918.
11. Selenin, W. P.: *Arch. f. d. ges. Physiol.* 143: 137, 1912.
12. Yacoel, J., and Papanayotou, D.: *Arch. d. mal. du coeur* 20: 24, 1927.

A NEW METHOD FOR CLINICAL DETERMINATION OF HUMAN CAPILLARY TENSION*

PHILIP STRAX, M.D., AND ARTHUR C. DEGRAFF, M.D.
NEW YORK, N. Y.

INTRODUCTION

A STUDY of the various methods for measuring capillary blood pressure in man reveals that most of them are inadequate for routine clinical investigation for one or both of two reasons: (1) They are not practicable in regard to clinical application. (2) The results obtained are not accurate. To be available clinically, a method must have neither of the above faults. We have devised a new instrument and a new technic which, we believe, fulfill both requirements.

REVIEW OF PREVIOUS METHODS

Roy and Brown¹ (1875), although not studying human capillaries, deserve mention as the first to conceive a practical apparatus for the indirect measurement of the tension in capillaries as viewed with a microscope. With an air-filled capsule covered by a transparent animal membrane, pressure was applied to the capillaries in the web of a frog, as seen under the microscope. The principle of this method was used in modified form in the tonometers of many later investigators for application to man.

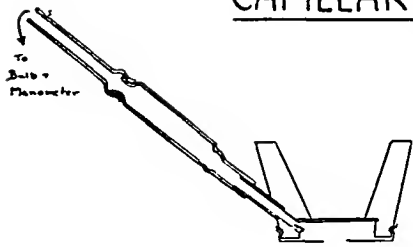
Methods for measuring human capillary pressure fall into two distinct categories: (1) those measuring so-called arteriocapillary pressure; (2) those attempting to measure actual capillary pressure.

In the first group, three methods are worthy of mention. Mosso² (1895) used a metallic glove filled with warm water over the middle and ring fingers. Pressure was applied through the medium of the water, and oscillations were transmitted to a kymograph. Oscillations of maximum amplitude were taken as the criterion of mean tension. Gaertner³ (1899) compressed the second phalanx of the finger by means of a pneumatic ring. On decompression, the instant of reappearance of redness was taken as the end-point for determination of capillary pressure. Kreidl⁴ (1902) employed, at the base of the nail, a half-ring attached to a lever, which oscillated on a drum, to obtain the so-called arteriocapillary pressure.

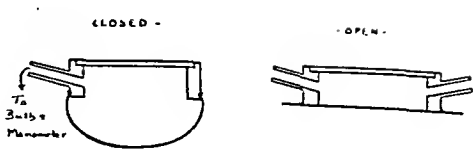
The readings obtained by these men were certainly not measurements of capillary pressure. Capillaries do not show the oscillation

*From the Department of Medicine, University and Bellevue Hospital Medical College, New York University, and the Third (New York University) Medical Division of Bellevue Hospital.

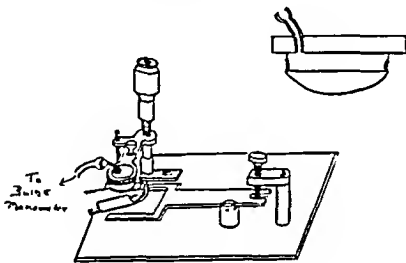
METHODS USED IN DETERMINATION
OF
CAPILLARY BLOOD PRESSURE
INDIRECT METHODS



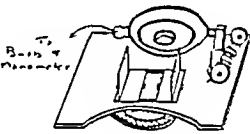
A. LOMBARD



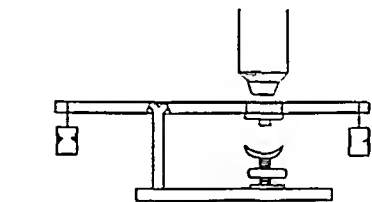
B. LEWIS & HAYNAL



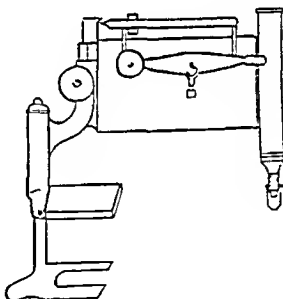
C. DANZER & HOOKER



D. KYLIN

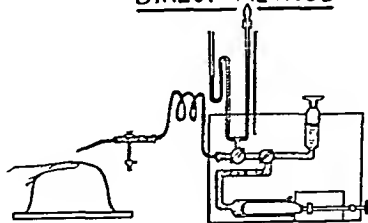


E. GUILLAUME



F. RAJKA

DIRECT METHOD



G. LANDIS

Fig. 1.—Previous methods used in determination of capillary blood pressure in man.

phenomena on which these methods were based. The actual figures obtained were about three times higher than those of capillary pressure as determined by later workers.

In the second group are those methods which purported to measure actual capillary pressure. These fall into two classes: (1) direct, (2) indirect.

The direct measurement of capillary pressure in man by actual intubation under control of a microscope was first undertaken by Carrier and Rehberg⁵ (1922).

Landis⁶ (1930) (*see* Fig. 1 *G*) devised a much more accurate method for micro-injection of the human capillary. A micropipette with an orifice of 8-12 micra in diameter is used. It is controlled by a Chambers' micromanipulator which is capable of moving it in three planes. The pipette is filled with fluid from a reservoir and connected to a manometer. Pressure is applied until only a few corpuscles remain oscillating at the tip of the pipette. A reading is then taken.

This method is probably the most accurate of all to date. Unfortunately, it is not adaptable to clinical use. It requires an extremely high degree of skill on the part of the operator, and an even higher degree of patience on the part of the subject. Special training is necessary to operate the micromanipulator successfully. To apply it to micro-injection of human capillaries is a task for the expert. Then, too, before insertion of the pipette into a capillary, it is always necessary to remove a thin layer of epidermis with a keen razor blade. Even with this precaution, the author states, breakage occurs frequently. Landis' apparatus, however, obviates many technical errors of the method of Carrier and Rehberg, so that the results obtained may be taken as the standard measurement of capillary pressure in the human. It follows, then, that only those instruments which give results comparable to those of Landis are sufficiently accurate.

Another form of the direct method of measuring capillary pressure is that of Basler⁸ (1914) and Weiss⁹ (1914). These men pricked the finger and applied to the bleeding point a tube filled with warm salted serum plus hirudin. In the tube was a piston which could slide up and down easily. By maneuvering the piston, the pressure necessary just to stop bleeding could be determined. The criticism of this method is obvious. The equilibrated pressure cannot be proved to be capillary. The bleeding probably comes from arterioles, capillaries, and venules of varying caliber. Problems in technic, such as proper sealing of the tube to the skin and prevention of clotting, add to the difficulties in using this method clinically.

Indirect methods for measuring capillary pressure fall into two groups: (1) those using blanching of the skin as an end-point; (2) those using as the end-point some phase of cessation of flow, as visualized microscopically.

Von Kries¹⁰ (1878) was the first to propose the use of color modifications in the skin to measure capillary pressure. He devised a simple movable stand which was applied to the skin at a definite area. Weights were added until blanching occurred. The method was later modified by von Basch¹¹ (1900) and by von Recklinghausen¹² (1906), who used glass capsules sealed to the skin and filled with air at measurable pressures. Basler¹³ (1912) devised an elastic closed capsule to apply pressure. The latter is interesting as the forerunner of later methods using elastic compression. More recently, Marks¹⁴ (1920) described a similar capsule. He asserted that compression with blanching as the end-point was the only clinical method then available for measuring capillary pressure. Ariola¹⁵ (1925) devised a similar instrument.

The results obtained by these methods cannot be accepted as accurate measurements of capillary pressure because: (1) It has been shown repeatedly by various workers (Danzer and Hooker¹⁶; Boas¹⁷; M. Weiss¹⁸) that initial blanching of the skin is due chiefly to an evacuation of the superficial venous plexuses. Skin blanching occurs before flow in the capillaries, as visualized microscopically, is affected. (2) Blanching of the skin does not offer a reliable end-point. The skin of different subjects shows a great variation in the amount of pigment it contains. Then, too, there is the great personal factor as to what constitutes initial blanching. The strongest evidence of the fallacy of the method is that different workers with the same device have obtained quite varying results (Friedenthal¹⁹).

Hill²⁰ (1920) applied pressure by focussing a fine jet of water on the skin at the nail-bed. The jet was slowly moved to and fro and the pressure slowly increased. Initial paling of the skin was taken as the end-point for capillary pressure determination. The hand was then raised to empty the veins, while a cuff on the arm compressed the arterial flow. The jet of water was again used to cause paling of the skin. The second reading was subtracted from the first to give the final result. As noted above, the results of Hill probably represent the pressure in the small venous plexuses of the skin rather than that in the capillaries or arterioles. Again, the difficulty of knowing what constitutes initial paling of the skin presents itself.

Lewis and Haynal²¹ (1928) (*see* Fig. 1 B), working on histamine flares in the human skin devised a method for measuring what they termed venule pressure. Histamine, when injected into the human skin, causes a local dilatation of the small arterioles, and, as these authors asserted, a passive dilatation of the capillaries. Three to twelve minutes after injection of histamine, pressure was applied to the reddened area through either an open capsule sealed to the skin or a closed capsule until blanching back to normal was secured. The readings obtained were taken to represent close approximations to capillary pressure.

The physiological basis of this method is disputed by Krogh and Rehberg,²² who maintain, on the basis of their work, that the capillary dilatation with histamine is an active one. Also, and what is more important, different workers with the device obtain widely varying results. Thus, Weiss and Ellis²³ (1929), using the same method, get measurements about one-fifth those of Lewis and Haynal. At any rate, it is difficult to see how a method which produces abnormal changes in the smaller vessels of the skin could be used to measure accurately the normal pressure in these vessels.

Most of the modern methods for measuring capillary pressure utilize visualization of the capillaries in the nail-bed as a basis.

Heuter²⁴ (1879) was the first to observe living capillaries in the human. Lombard²⁵ (1911) was the first to put this observation into practice by utilizing it in measuring capillary pressure. He placed a drop of glycerine at the base of the nail, focussed on the area with a microscope with a magnification of 65x, and saw entire capillary loops with the streaming of corpuscles in them. Anatomically, the capillaries in the skin papillae are arranged vertically everywhere except at the base of the nail, where they lie more or less horizontally. For this reason, only the top of the capillary loop can be seen in other parts, while at the base of the nail the entire loop can be examined (Spalteholz²⁶; Callander²⁷).

Lombard (*see* Fig. 1 A) applied pressure to the skin by means of an open capsule filled with glycerine. Glycerine is a very poor medium for conducting pressure. Because of its high viscosity, pressure changes are transmitted only slowly. Krauss²⁸ (1914) used a chamber covered at one end by goldbeater's skin. Pressure was applied by means of a bulb connected to a manometer which measured the tension. A magnification of 10x was used. Although Krauss claimed to see the cutaneous vessels, his index was probably skin blanching. Danzer and Hooker¹⁶ (1920) (*see* Fig. 1 C) devised a method based on the principles of the Krauss instrument. They employed a capsule which was less cumbersome, but which was also covered by goldbeater's skin. A microscope was used to determine their end-point. Kylin²⁹ (1921) (*see* Fig. 1 D) also constructed an instrument on similar principles, differing only in size and form of construction. The results obtained by these methods correspond closely, and are probably as accurate as can be obtained by the indirect method. Clinically, however, these instruments present two important practical difficulties. Goldbeater's skin, made from the outer coat of the cecum of an ox, is not readily procurable in this country. The technic of making it transparent is difficult and, even in experienced hands, about 80 per cent of the prepared membranes are unfit for use. When employed with best precautions, the skin collects dust and clouds comparatively quickly. Since it cannot be cleaned satisfactorily, it is then of little value. Furthermore,

these methods require the services of two men, one to watch the capillaries, the other to apply and record the pressure. Thus, we found these methods not to be as clinically practicable as their author claimed.

The use of an elastic membrane for transmitting pressure has been attacked more recently. It has been maintained by Guillaume³⁰ (1924) and Rajka³¹ (1926) that all the pressure produced is not transmitted to the capillary because of the loss on the sides of the finger due to elasticity of the membrane. These workers also have asserted that to be available as a clinical method any device for measuring capillary pressure should be operable by one man. Guillaume (*see* Fig. 1 *E*) constructed a simple lever from which projected a small piece of glass of known area which made contact with the finger. At the end of the lever was a cup into which weights could be dropped to apply pressure. Unfortunately, there was no simple means of grading the pressure applied. To get accurate results would necessitate considerable manipulation of weights with attendant consumption of time. Rajka (*see* Fig. 1 *F*) devised a complicated device for applying pressure through a rigid surface. The great amount of inertia in the system probably explains his low readings. It is obvious that capillary pressure must be higher than venous pressure. The figures obtained by this investigator are lower than the accepted values for venous pressure. Besides, this method requires too complicated a device for practical work.

Measurements of normal human capillary pressure as obtained by these various methods are:

| | | |
|---|------|---------------|
| I. Measurement of arteriocardillary pressure: | | |
| a. Mosso ² | 1895 | 60-70 mm. Hg. |
| b. Gaertner ³ | 1899 | 60-80 |
| c. Kreidl ⁴ | 1902 | 55-65 |
| II. Measurement of actual capillary pressure: | | |
| A. Direct methods: | | |
| 1. Intubation methods: | | |
| a. Carrier and Rehberg ⁵ | 1922 | 4.5-7.5 |
| b. Landis ⁶ | 1930 | 12-32 |
| 2. Bleeding methods: | | |
| a. Basler ⁸ | 1914 | 7.7-13 |
| b. Weiss ⁹ | 1914 | 10 |
| B. Indirect methods: | | |
| 1. With skin blanching: | | |
| a. Using normal skin coloration: | | |
| (1) von Kries ¹⁰ | 1878 | 24-38 |
| Natanson ³² (von Kries method) | 1886 | 71 |
| (2) von Basch ¹¹ | 1900 | 25-30 |
| (3) von Recklinghausen ¹² | 1906 | 55 |
| Krogh and Rehberg ²² (von Recklinghausen method) | | |
| (4) Basler ¹³ | 1928 | 5- 8 |
| Landerer ³³ (Basler method) | 1912 | 7- 9 |
| Goldman ³⁴ (Basler method) | 1913 | 17-25 |
| (5) Marks ¹⁴ | 1914 | 5- 7 |
| (6) Hill ²⁰ | 1920 | 6-20 |
| (7) Ariola ¹⁵ | 1920 | 10 |
| | 1925 | 10-14 |

| | | |
|--|------|-------|
| b. Using histamine flares: | | |
| (1) Lewis and Haynal ²¹ | 1928 | 50-60 |
| (2) Weiss and Ellis ²³ | 1929 | 6-12 |
| 2. With direct visualization of capillaries: | | |
| a. Pressure applied by rigid surface: | | |
| (1) Lombard ²⁵ | 1911 | 30-45 |
| (2) Guillaume ³⁰ | 1924 | 18-28 |
| (3) Rajka ³¹ | 1926 | 1- 2 |
| b. Pressure applied by elastic capsule: | | |
| (1) Krauss ²⁸ | 1914 | 10 |
| (2) Danzer and Hooker ¹⁶ | 1920 | 20-24 |
| Boas ³⁵ (Danzer and Hooker method) | 1922 | 20-30 |
| (3) Kylin ²⁹ | 1921 | 13.6 |
| Rowinger ³⁶ (Kylin method) | 1923 | 8 |
| Liebesny ³⁷ (Kylin method) | 1923 | 32.5 |
| Nevermann ³⁸ (Kylin method) | 1924 | 6-11 |
| Grzechonriak ³⁹ (Kylin method) | 1924 | 6-14 |

A glance at the foregoing table reveals the markedly varying results which investigators using the same or similar methods have obtained. The discrepancies are probably best accounted for by: (1) differences in the criteria of the end-point of a determination; (2) marked differences in the time required to take a reading—a fact which has an important bearing on the accuracy of the results, as will be indicated presently.

It would appear, therefore, that an indirect method which permits of a definite end-point and which also enables even an unskilled operator to take a reading in a very short time, would be the method of choice for routine clinical application—provided that it were shown to be sufficiently accurate. We have devised a new method for the clinical determination of human capillary pressure, which, in our opinion, meets these requirements.

APPARATUS AND METHOD

Essentially the apparatus consists of a lever (Fig. 2 *D* [a]), a spring (d), a finger rest (e), and a scale (c). The lever is approximately 20 cm. long. At one end it contains a circular plate of glass (b) to which is attached a smaller plate of glass (f), 2 mm. in diameter. Between the glass and the fulcrum, a screw is inserted into the lever which has attached to it a spring (d), the other end of which is attached to the base of the instrument. On the lever rests a movable rider (g), used in calibration of the instrument. The pointer of the lever is in proximity to a scale. A rest (e) is provided for the finger, which can be raised or lowered at ease in a vertical plane to bring the latter into proper relationship to the glass (f). The lever can be kept level by adjustment of the screw which regulates the tension of the spring.

The instrument can be placed conveniently on the stage of a microscope and clamped there to prevent movement. Reflected light is used. The stronger the light concentrated at the point of examination, the clearer the view of the capillaries obtained. Good results, how-

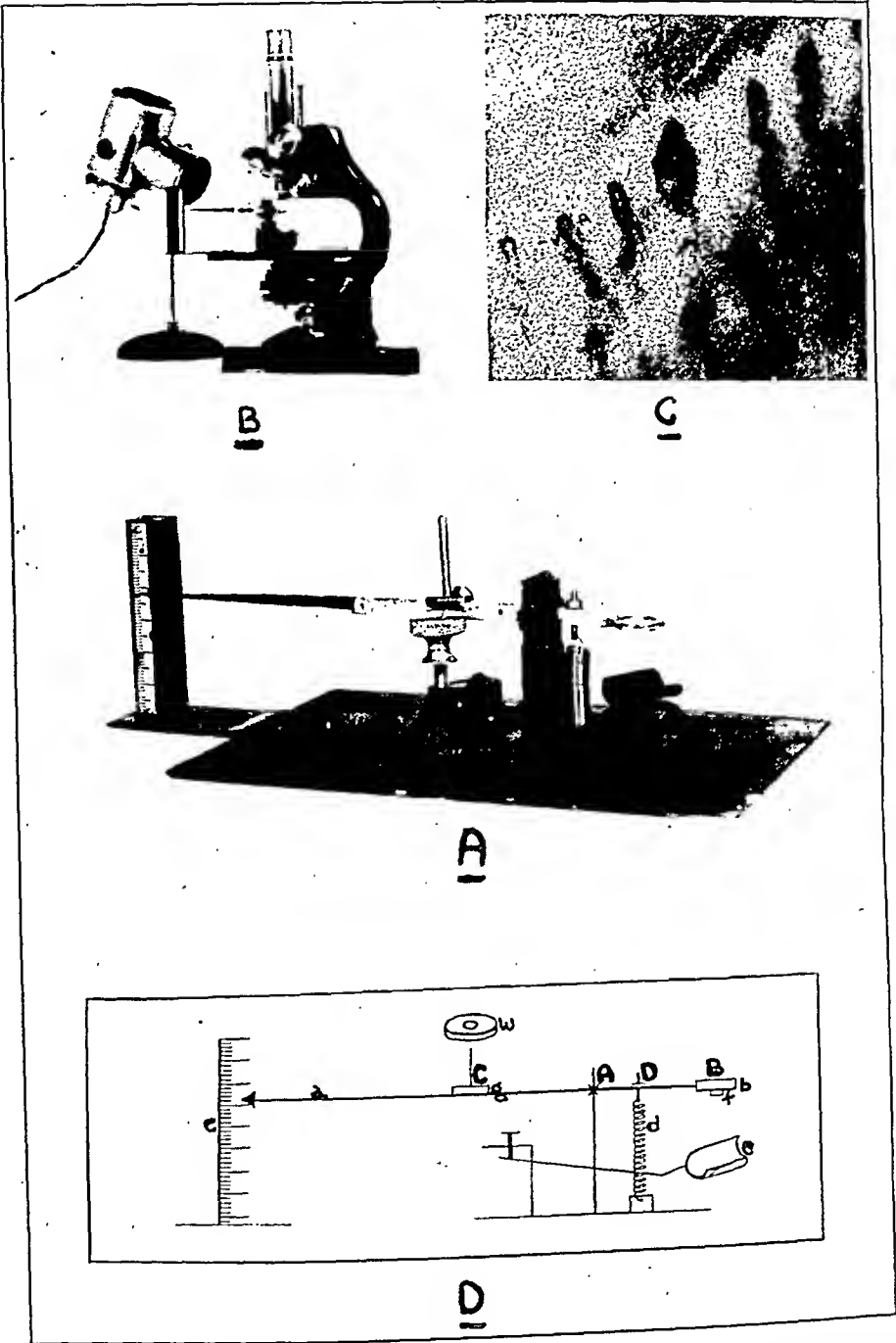


Fig. 2.—A. Photograph of the authors' clinical tonometer for measuring human capillary blood pressure. B. The instrument on a microscope stage ready for use. C. Photograph of the capillaries at the nail-bed, showing (a) arterial loop and (v) venous loop. D. Sketch showing the principles of construction of the instrument.

ever, can be obtained by placing an ordinary microscope lamp on the base of the instrument, which is on the stage of the microscope, so that the light is concentrated on the finger. A magnification of about 90-100 \times is used.

Calibration of the instrument is simple. A known weight (w) is placed on the rider which is on the lever. Then we know that:

$$\begin{aligned} 1. AD \cdot X_1 &= AC \cdot w \\ \text{and } 2. AD \cdot X_2 &= AB \cdot P \\ \text{whence } 3. P &= X_2 \left(\frac{AC \cdot w}{AB \cdot X_1} \right) \end{aligned}$$

where AD , AC , and AB are distances in cm. along the lever; X_1 is the deflection in cm. caused by the weight on the rider; X_2 is the deflection in cm. caused by the measurement of capillary pressure; and P is the weight in grams pressing on the capillaries. To change P from weight in grams to pressure in grams per square centimeter, the right side of equation 3 is divided by the area of the glass (f) which is in contact with the finger. The equation then becomes:

$$4. \text{ Pressure (gm./sq. cm.)} = X_2 \left(\frac{AC \cdot w}{AB \cdot X_1 \cdot R} \right)$$

where R is the area in square centimeters of the glass (f). Since pressure in grams per square centimeter is equal to pressure in centimeters of water, to change the reading to millimeters of mercury pressure, the right side of the equation is divided by the factor 1.36.

The rider is so placed on the lever that AC equals AB , thus simplifying the formula. It now becomes:

$$5. \text{ Pressure (mm. Hg.)} = X_2 \left(\frac{w}{X_1 \cdot R} \right) \div 1.36$$

The quantities w and R are known and constant. In short, to calibrate the instrument at any time, the weight is placed on the rider, the amount of deflection caused is noted and by simple arithmetic a factor is found which when multiplied by the deflection obtained in measuring capillary pressure gives the pressure directly in mm. Hg. The instrument which is pictured herewith is calibrated so that each mm. on the scale equals 2 mm. Hg. pressure.

A reading is taken as follows. The patient is at rest in the sitting posture with his hand, well supported, at heart level, to obviate differences due to hydrostatic pressure. A drop of cedarwood oil is placed on the finger at the nail-bed. The finger is placed on the rest (e), and raised by means of the screw so that the glass (f) comes in contact with the skin at the nail-bed. By watching the movement of the lever on the scale, the point of contact is easily determined. The microscope is then focussed on the capillary bed through

the glass (b). Pressure is easily applied by means of the screw, raising the finger rest against the lever. The other hand manipulates the focus of the microscope. When the end-point is reached, the pressure applied is read off directly on the scale in mm. Hg. One person can easily make a reading.

Readings are taken on two or three capillaries in the same finger and the results averaged. The finger of choice, we find, is the ring finger, because it is usually the best preserved as far as the skin at the nail-bed is concerned. The procedure is repeated on the middle finger, and the results of both fingers are averaged as the mean capillary tension. With a little practice, the entire process need not take more than five to ten minutes.

As an end-point we use the initial slowing in a medium-sized capillary. Only the more superficial capillaries are used; that is, those which come into view first. Initial slowing is not a difficult end-point because appreciable slowing is rather sudden in occurrence. Flow does not seem to be impaired until a certain amount of pressure is applied, when an abrupt slowing takes place. The reasons for choosing the end-point we did are: (1) It is definite. Readings on the same capillary several times give almost identical results. During a pressure determination a point is reached when a slight increase in pressure applied causes a marked slowing in capillary flow. This point remains more or less constant in successive readings. (2) It is accurate. Pressure applied on the outside of a capillary has no effect on its caliber or flow until it equals the pressure within the vessel. When the latter situation occurs, the flow is hindered. Increased extravascular pressure hinders the flow progressively until complete cessation occurs. It is obvious, then, that the most accurate end-point is the initial change in rapidity of flow. As mentioned above, this change, fortunately, is rather sudden, thus making it available as a convenient and definite end-point.

The results obtained by Landis,⁶ using the method of direct micro-injection of capillaries, are probably the most accurate representations of true capillary pressure, as indicated above. The fact that our results correspond closely to his is an important bit of evidence that our instrument is accurate, and that our end-point is correct.

To determine whether the factor of skin elasticity played an appreciable part in indirect measurement of capillary pressure, we took readings on men and women with varying textures of skin at the nail-bed. Readings did not differ materially. This finding is in accordance with those of other investigators using indirect methods. (Danzon and Hooker¹⁶; Boas.³⁵)

Besides being very convenient, the fact that readings can be taken rapidly increases the accuracy of the results. Initial pressure applied falls on the superficial venous plexuses, causing a retardation of flow

and back-pressure to the capillaries, increasing the tension in the latter vessels. The greater the delay in raising the external pressure to that within the capillaries, the greater the back-pressure. The short time which is consumed in taking a reading with our instrument practically obviates this difficulty.

RESULTS

Readings were taken on fifty subjects. Of these, thirty were not hospitalized, and twenty were confined to the hospital for conditions unrelated to the cardiovascular, renal, or pulmonary systems. All the subjects had diastolic blood pressures between 60 and 80, and systolic blood pressures between 110 and 130 mm. Hg. The group consisted of forty males and ten females. The temperature of the room in which observations were made was about 20° C. Determinations were made on fingers which were normally warm.

An example of how results were tabulated follows.

P. M., normal white male, aged 24 years. Temperature of room—18° C. Fingers normally warm. Texture of skin soft. Blood pressure—124/76. Capillary pressure:

| | | |
|------------------|------------|--------------------|
| 1. Ring finger: | | |
| a. 1st capillary | 22 mm. Hg. | Average—22 mm. Hg. |
| b. 2nd capillary | 24 | |
| c. 3rd capillary | 20 | |

| | | |
|-------------------|------------|--------------------|
| 2. Middle finger: | | |
| a. 1st capillary | 24 mm. Hg. | Average—21 mm. Hg. |
| b. 2nd capillary | 19 | |
| c. 3rd capillary | 20 | |

Mean capillary pressure: 21.5 mm. Hg.

Variations in readings on the same individual in different capillaries were slight:

5 cases showed a variation of 0-1 mm. Hg.

32 cases showed a variation of 2-3 mm. Hg.

13 cases showed a variation of 4-5 mm. Hg.

Results obtained in the series of fifty individuals were as follows:

20 per cent of the readings were 18-21 mm. Hg.

70 per cent of the readings were 22-25 mm. Hg.

10 per cent of the readings were 26-29 mm. Hg.

It will be seen that these results correspond closely with those obtained by Landis.

SUMMARY

1. Methods for the determination of human capillary pressure have been reviewed and criticism has been attempted from the viewpoints of accuracy and of clinical applicability.

2. A device is described which is easily applicable to routine clinical use. The results obtained fall well within those obtained by the

method of direct intubation of Landis, thus leading us to believe that they are substantially accurate.

3. The average capillary pressure, in the normal individual we find to be 18-29 mm. Hg.

The authors wish to express their appreciation of the efforts of Dr. Roger S. Estey, who carefully examined and corrected the physical principles of the instrument, and of Klett Mfg. Co. in New York City, who constructed the instrument.

REFERENCES

1. Roy, C. S., and Brown, G.: Blood Pressure and Its Variations in Arterioles, Capillaries, and Smaller Veins, *J. Physiol.* 2: 323, 1875.
2. Mosso, A.: Sphygmomanometre pour mesurer la pression sang chez l'homme. *Arch. ital. de biol.* 23: 177, 1895.
3. Gaertner, G.: Ueber einen neuen Blutdruckmesser, *Wien. klin. Wchnschr.* 12: 696, 1899.
4. Kreidl, A.: Quoted by Bouloumie, P.: Oscillations capillaires et leur mensuration par l'appareil de Kreidl. *Bull. gén de thérap. Paris* 147: 49, 1904.
5. Carrier, E. B., and Rehberg, P. B.: Capillary and Venous Pressure in Man. *Skandin. Arch. f. Physiol.* 44: 20, 1923.
6. Landis, E. M.: Micro-Injection Studies of Capillary Blood Pressure in Human Skin. *Heart* 15: 209, 1930.
7. Chambers, R.: New Apparatus and Methods for the Dissection and Injection of Living Cells, *J. Roy. Mic. Soc.* 373, 1922.
8. Basler, A.: Untersuchungen ueber den Druck in den kleinsten Blutgefäßen der menschlichen Haut, II. Mitt., *Arch. f. d. ges. Physiol.* 157: 345, 1914.
9. Weiss, E.: Ein neuer Apparat zur blutigen Kapillardruckmessung, *Zentralbl. f. Physiol.* 28: 375, 1914.
11. von Basch, S.: Ueber die Messung des Capillardruckes im Menschen und deren physiologische und klinische Bedeutung, *Wien. klin. Rundschau.* 14: 549, 1900.
12. von Recklinghausen, H.: Unblutige Blutdruckmessung, *Arch. f. exper. Path. u. Pharmakol.* 55: 463, 1906.
13. Basler, A.: Untersuchungen ueber den Druck in den kleinsten Blutgefäßen der menschlichen Haut, I. Mitt., *Arch. f. d. ges. Physiol.* 147: 393, 1912.
14. Marks, H. E.: Clinical Determination of Venous and Capillary Pressure, *M. Clin. North America* 4: 239, 1920.
15. Ariola, V.: Nuovo Misuratore della Pressione Capillare, *Riforma med.* 41: 314, 1925.
16. Danzer, C. S., and Hooker, D. R.: Capillary Blood Pressure in Man Using Microtonometer, *Am. J. Physiol.* 52: 136, 1920.
17. Boas, E. P., and Mufson, I.: Capillary Blood Pressure in Hypertension and in Nephritis, *J. Lab. & Clin. Med.* 9: 152, 1923.
18. Weiss, M.: Capillary Pressure, *Presse méd.* 31: 211, 1923.
19. Friedenthal, H.: Ueber Kapillardruckbestimmung, *Ztschr. f. exper. Path. u. Ther.* 19: 222, 1918.
20. Hill, L.: Capillary Pressure, *J. Physiol.* 54: xciii, cxxxiii, 1920.
21. Lewis, T., and Haynal, I.: Capillary Pressure and Tone, *Heart.* 14: 177, 1928.
22. Krogh, A., and Rehberg, P. B.: Reflex Flare, *J. Physiol.* 64: 32, 1928.
23. Weiss, S., and Ellis, L.: Measurement of Capillary Pressure Under Natural Conditions, etc. *J. Clin. Investigation* 8: 47, 1929.
24. Hentér, C.: Die Cheilo-angioskopie, eine neue Untersuchungs-methode zu physiologischen und pathologischen Zwecken, *Centralbl. f. d. med. Wissen.* 13: 225, 1897.
25. Lombard, W. P.: The Blood Pressure in Arterioles, Capillaries, and Small Veins of Human Skin, *Am. J. Physiol.* 29: 335, 1912.
26. Spalteholz, W.: Die Verteilung der Blutgefäße in der Haut, *Arch. f. Anat. u. Physiol. (Anat. Abt.)* p. 1, 1893.
27. Callander, C. L.: Photomicrographic Studies of Morphology of Surface Capillaries in Health and Disease, *J. A. M. A.* 84: 352, 1925.
28. Krauss, H.: Der Kapillardruck, *Saunml. klin. Vortr. inn. Med.* 237/239: 315, 1914.
29. Kylin, E.: Eine Modifikation meines Kapillardruckmessers, *Zentralbl. f. inn. Med.* 42: 785, 1921.

30. Guillaume, A. C.: La Pression sanguine dans les capillaries, *Bull. méd.* #45 38:1217, 1924.
31. Rajka, E.: Ueber das Messen der Capillardruckes an der menschlichen Haut mit den Torok-Rajka-Wessely'schen Capillartonometer, *Ztschr. f. d. ges. exper. Med.* 48: 570, 1926.
32. Natanson, G.: Ueber das Verhalten des Blutdruckes in den Capillaren nach Massenmuseurungen, *Arch. f. d. ges. Physiol.* 39: 386, 1886.
33. Landerer, R.: Zur Frage des Kapillardruckes, *Ztschr. f. klin. Med.* 78: 1, 1913.
34. Goldmann, E.: Ueber die Beeinflussung des Blutdruckes den Kapillaren der Haut durch verschiedene Temperaturen, *Arch. f. d. ges. Physiol.* 159: 51, 1914.
35. Boas, E. P.: Capillary Pressure in Acrocyanosis, *J. A. M. A.* 79: 1404, 1922.
36. Rominger, E.: Ein Beitrag zur Physiologie und Pathologie des Kreislaufs, *Arch. f. Kinderh.* 198: 215, 1923.
37. Liebesny, P.: Untersuchungen ueber die Capillardruckmessung, *Arch. f. d. ges. Physiol.* 198: 215, 1923.
38. Nevermann, H.: Capillardruckmessungen, *Klin. Wchnschr.* 3: 1433, 1924.
39. Grzechouriak, F.: Der Kapillardruck besonders während der Schwangerschaft und im Wochenbett, *Ztschr. f. Geburtsh. u. Gynäk.* 87: 128, 1924.

Department of Clinical Reports

CORONARY THROMBOSIS WITH COMPLETE HEART-BLOCK AND RELATIVE VENTRICULAR TACHYCARDIA A CASE REPORT*

AUDLEY O. SANDERS, M.D.
PALO ALTO, CALIF.

THOUGH Levine¹ states that with coronary thrombosis almost any form of cardiac irregularity may be found, he also states that one of the more uncommon occurrences is the development of complete heart-block. In the 145 cases of coronary thrombosis which he reports, complete heart-block was known to have occurred in but two cases. In one of these a ventricular rate of 28 was recorded. The ventricular rate of the other case is not given. He reports that paroxysmal ventricular tachycardia developed in five cases of this series.

Numerous cases of complete heart-block with ventricular tachycardias have been reported as developing in patients who were receiving massive doses of digitalis,^{2, 3, 4, 5} and it has been generally accepted that the digitalis was a causative factor in the production of these ventricular tachycardias—of the ventricular tachycardias of the “supra-ventricular form” as well as of the paroxysmal form. However, in 1928, Carr and Reddick⁴ reported a case of complete heart-block with an auricular rate of 110 and a ventricular rate of 83 in a young woman, with mitral disease and acute arthritis, who had not received digitalis. Other and similar though less definite cases have been reported, but without statements as to digitalis medication. It therefore seems possible that relative ventricular tachycardia may not be of rare occurrence in cases of complete heart-block where digitalis can be entirely excluded as a causative factor. Such a case is here reported.

CASE REPORT

A practising physician, 56 years of age, who for many years had considered himself to be in perfect health, was taken suddenly, while driving home to lunch, with an agonizing pain in the region of the lower part of the sternum. He was able, however, to control his automobile until he reached his home, which was but a short distance away. His wife helped him from the street to the house and saw that he was very ill. About this time he began to vomit, and he fell to the floor as he entered the house. A neighboring physician was at his side in a few moments. This physician carried the sick man to a bed and thought that he was dying. His radial pulse was not palpable and his heart sounds were very faint.

*Published with the permission of the Medical Director of the U. S. Veterans Bureau.

I was called to the sick man's bedside about thirty minutes after the onset of the attack. He lay propped up on pillows, between wide open windows. It was very evident that he was in extreme shock and in great distress; his color was ashen and he was drenched with sweat. However, he had no notable dyspnea. His complaint was of an agonizing pain which centered behind the lower part of his sternum and extended to both arms. He said that the pain in the arms was even

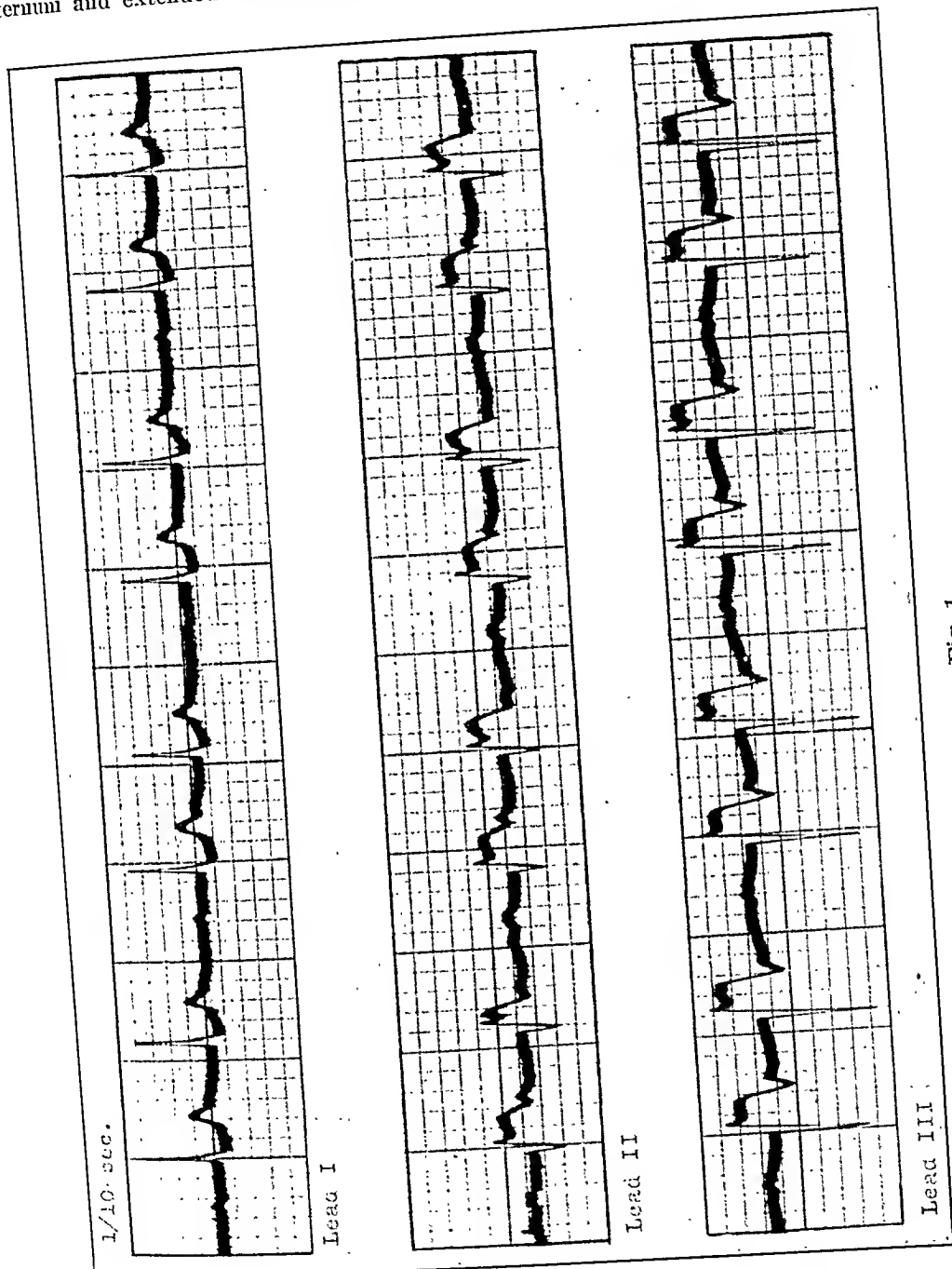


Fig. 1.

more severe than was the pain in the region of the sternum. The radial pulse was now 44 and quite regular, but very soft. The heart sounds were faint, but the ventricular rate was the same as that of the radial pulse. It was, however, observed at this time that the visible impulses of the external jugulars seemed to have twice the rate of the arterial pulse.

One or more nitroglycerin tablets had already been given, with no relief. After the contents of several ampules of amyl nitrite had been inhaled to no effect, a

quarter of a grain of morphine was given hypodermically. The morphine controlled the pain rather well. He slept a little and then remained quiet for about two hours. From that time morphine was given freely in the attempt to control the pain which continued to be severe. For some five or six hours, throughout the afternoon, the pulse remained at 44 and the rhythm continued quite regular. The pulse became much stronger and the heart sounds became somewhat clearer as the

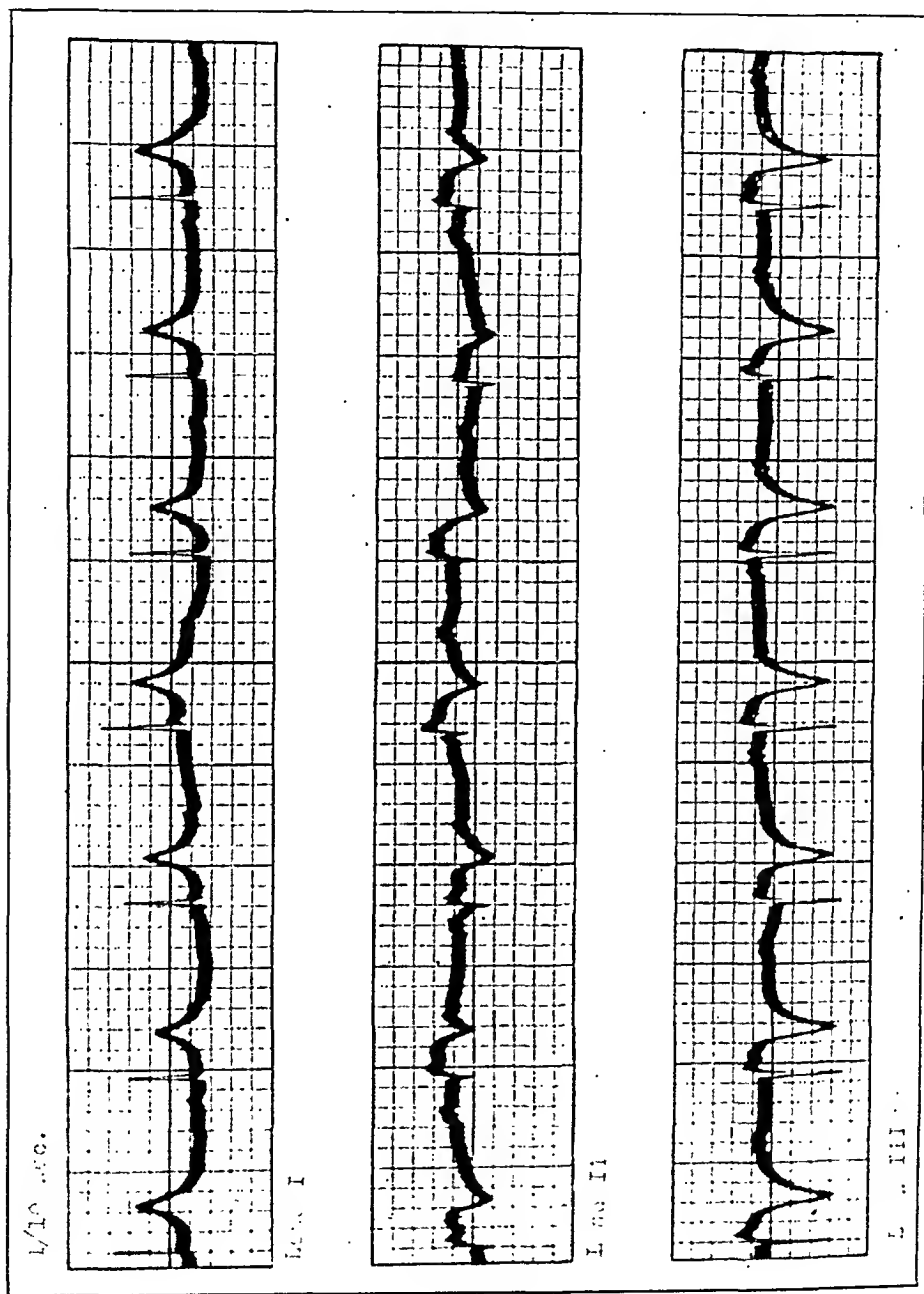


FIG. 2.

and there were occasional dropped beats at irregular intervals. afternoon advanced. Early in the evening, the pulse rate increased to about 70

Though the sick man had morphine during the night, he rested very badly, and his chest and arm pains were very distressing. He was taken to the hospital early the next morning and electrocardiographic records (Fig. 1) were taken at 9 A.M. The electrocardiograms showed an advancing, 3-to-2 heart-block, together with the

characteristic evidences of coronary thrombosis. A leucocyte count was reported as 12,000. At 3 p.m. the temperature was 99°; in the evening it was higher. All later temperature records showed elevations above normal. On the morning of the second day in the hospital the leucocyte count was 16,000. A blood Wassermann was reported negative. The second electrocardiographic records (Fig. 2) were taken on the morning of the second day in the hospital. These electrocardiograms showed complete heart-block with an auricular rate of 120 and a ventricular rate of 70, each rate being quite regular.

During the patient's second day in the hospital, to-and-fro pericardial friction sounds were heard. He complained now of severe pain in his neck, in addition to the chest and arm pains. He was also much distressed by abdominal "gas pains," and his respirations were labored. He grew steadily worse and died at 7:30 A.M., the third day in the hospital.

This patient received no digitalis or any other heart stimulant prior to or during his final illness.

Autopsy.—The body was that of a small man, 56 years of age. The pericardial fluid was slightly increased and cloudy. A thin, shaggy layer of fibrinous material was attached to the anterior surface of the heart. The major portion of that area which represented the surface of the right ventricle showed the dark purplish discolorations characteristic of infarction. The heart weighed 260 grams. The cardiac valves were all quite normal. No mural thrombi were found. The infarction seemed to involve the greater portion of the outer wall of the right ventricle, recent, degenerative changes being found by section to extend to the apex and to the interventricular septum, both anteriorly and posteriorly. No definite, degenerative changes were found involving the left ventricular myocardium. No fibrous areas suggestive of old myocardial lesions were found. The aorta was smooth and quite free from atheromatous changes. The coronary openings were unobstructed. However, on dissection of the right coronary artery, it was found to be much thickened, hard and slightly nodular, though the lumen seemed to be unobstructed for the first 2 cm. Then, a recent, dark thrombus was encountered. This thrombus was traced well into the infarcted myocardium. On dissection of the left coronary artery the walls were found to be remarkably soft and normal in appearance, no sclerotic changes being evident.

COMMENT

Clinical observations made soon after the onset of the attack led to the impression that a 2-to-1 heart-block was present. It seemed that after a few hours the conduction improved to the extent that only an occasional auricular impulse failed to bring a response from the ventricles. On the second day conduction was progressively failing. On the third day complete A-V disassociation was present with a ventricular rate far in excess of that which is commonly assumed to be the inherent rate of contraction of the ventricular myocardium.

REFERENCES

1. Levine, Samuel A.: *Coronary Thrombosis: Its Various Clinical Features*, Baltimore, 1929, Williams and Wilkins Co.
2. Luten, Drew: *Clinical Studies of Digitalis*, Arch. Int. Med. 35: 74, 1925.
3. Howard, Tasker: *Double Tachycardia*, Am. J. M. Sc. 173: 164, 1927.
4. Carr, J. G., and Reddick, W. G.: *Conduction Disturbances in Acute Rheumatic Infections*, J. A. M. A. 91: 853, 1928.
5. Bloom, B., and Perlow, S.: *Complete Heart-Block Associated With Rapid Ventricular Rate. Report of Two Cases*, AM. HEART J. 5: 486, 1930.

AURICULAR FLUTTER IN A NEWLY BORN INFANT*

REPORT OF A CASE

JAMES G. CARR, M.D., AND WILLIAM B. MCCLURE, M.D.
EVANSTON, ILL.

AURICULAR flutter is an infrequent event in children. In 1929 Willius and Amberg¹ reviewed the literature of paroxysmal tachycardia in children. They found reports of only six cases of auricular flutter. The youngest patient in the latter group was an infant of three months. Sir Thomas Lewis² reported the case in 1915. We have found no reports of other cases of flutter in children since the publication of the paper of Willius and Amberg.

Dressler and Löwy³ believe that many of the cases reported as auricular paroxysmal tachycardia are in reality cases of flutter, and make this statement: "The reports of cases in which no graphic registration is included appear to justify the opinion that here we are usually dealing with flutter, inasmuch as the pulse frequency observed in these cases is often of such a height (220-260) as is commonly found only in flutter." Even though this surmise may be correct the incidence of flutter in childhood is far from common.

In this connection, reference should be made to the cases of paroxysmal tachycardia reported by de Bruin⁴ and by Doxiades⁵ since Willius and Amberg published their paper. De Bruin's case was one of paroxysmal tachycardia in an infant of five weeks. The cardiac rate was 280. An electrocardiogram was not obtained. Doxiades reported four paroxysms of tachycardia in an infant beginning when the patient was seven days old. In the second attack the rate was 240. The electrocardiogram was interpreted as that of an auricular tachycardia, but it is significant that the rate after the subsidence of the attack was half that of the rate during the paroxysm.

The case which we are reporting is the first, so far as we can find, in which the flutter was present at birth. The cardiac irregularity was noted occasionally before birth.

REPORT OF CASE

A white female infant, weighing 10 lb. 13½ ounces, was born at term by cesarean section on October 29, 1930. Dr. Charles E. Galloway, the obstetrician, states that the mother had had periods of uterine bleeding during early pregnancy which necessitated her remaining in bed most of three months (February 28 to June). During frequent examinations up to September 16 no abnormal fetal

*From the Department of Medicine of the Evanston Hospital.

heart sounds were noted. On October 7 the fetal heart tones were very irregular, of a variable type which was unlike any other fetal heart irregularity which he had ever heard. Dr. Galloway considered it an exaggerated sinus arrhythmia. During uterine contractions of labor, the irregularity became accentuated and at times the heart tones could scarcely be heard. Following rupture of the membranes, the heart tones were not heard for about five minutes. When labor had lasted thirty hours, with complete dilation of the cervix but without engagement of the head, and with the fetal heart sounds irregular, cesarean section was done.

On September 30, Dr. Philip H. Smith found the fetal heart rate about 160 per minute with some irregularity of a constant type. On two occasions during

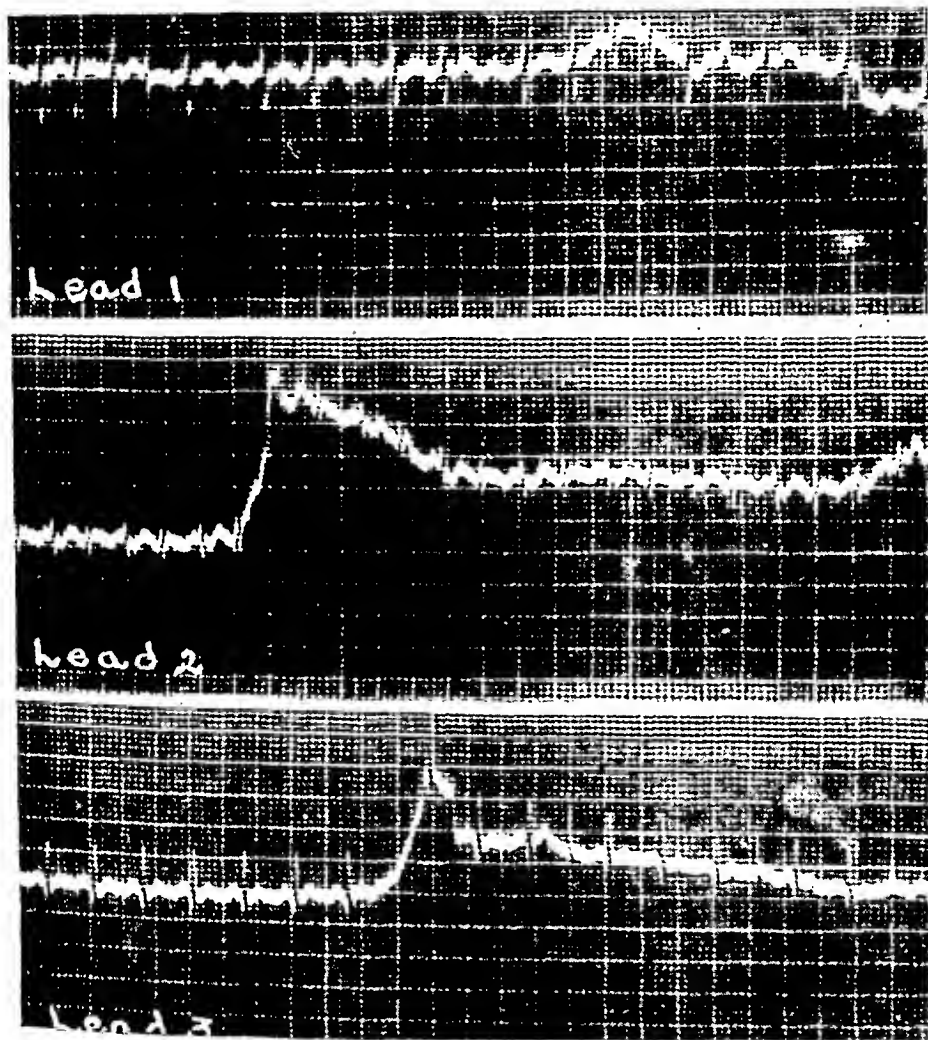


Fig. 1.—Electrocardiogram taken October 30, 1930, about twenty-six and one half hours after birth. Note flutter, with irregular block in Lead 1.

labor he examined the fetal heart and noted a marked variable irregularity which he interpreted as sinus arrhythmia. This irregularity was different from that which is often heard at the end of the second stage of labor when the baby is in distress.

At birth, at 8:16 A.M., October 29, because breathing was somewhat slow in starting, resuscitative measures were used, after which the baby's color was good.

The infant was first seen by one of us (McClure) at this time, about six minutes after birth. The respiratory movements were rapid. The heart beats were about 180 a minute, with marked arrhythmia at times; there were also short periods of a much more rapid rate, and of a much slower one. No murmur was heard, and except for the abnormal heart action and rapid breathing, the infant seemed normal.

At 5:30 P.M. the respiratory rate was 60 a minute. The heart rate and rhythm were still variable and were definitely influenced by the deeper respiratory movements.

At 9:30 A.M., October 30, the heart sounds were regular for longer intervals with the rate between 188 and 192 a minute. When the infant held her breath momentarily before crying, there was a marked slowing with a gallop-like rhythm for a few beats, with a return to regular, rapid beats when she relaxed. The baby had regurgitated dextrose solution feedings during the night.

At 5:15 P.M., October 30, while the infant was sleeping, the respirations were 65 a minute and the heart sounds which were regular, were 192 a minute. Irregularity occurred only when she was awake and crying.

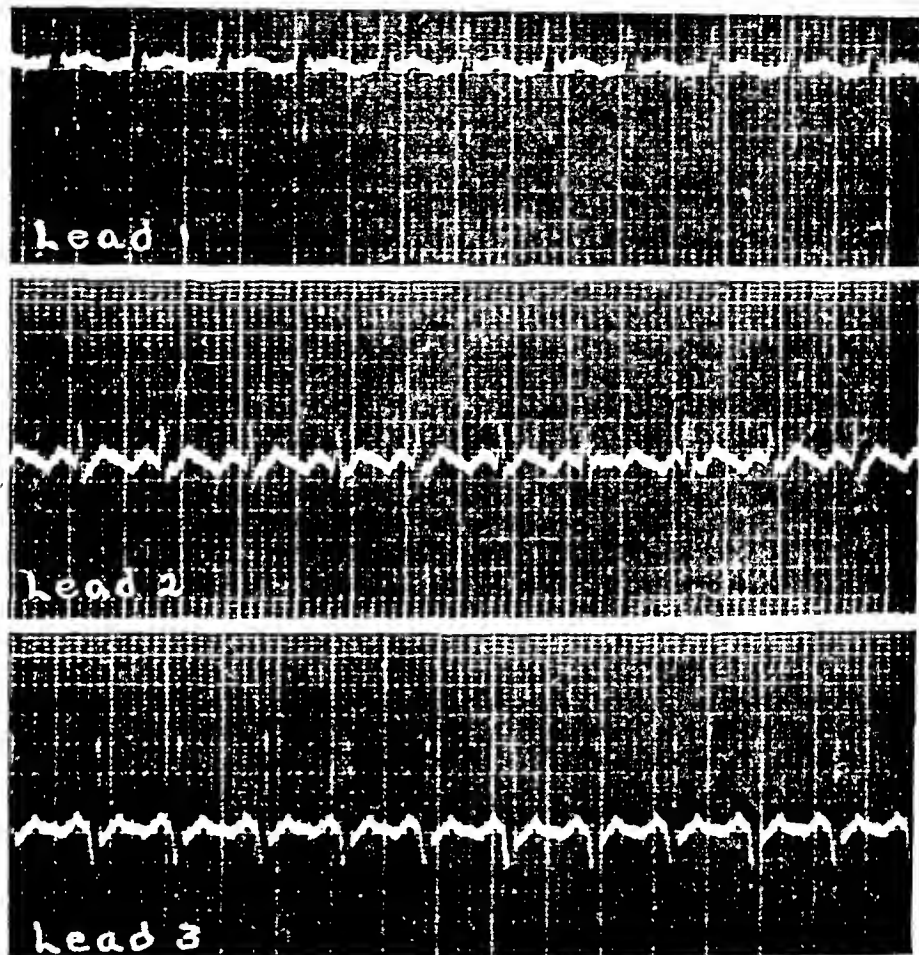


Fig. 2.—Electrocardiogram taken October 31, 1930, with motor speeded up. Flutter with 2-1 rhythm: 3-1 noted once in Lead II.

At 10:45 A.M., October 31, the infant's color was good. The heart beats were 192 a minute, becoming irregular when the child moved and made sounds. The respiratory rate was 60 to 64 a minute. During the previous night, on two occasions, the baby had manifested cyanosis about the mouth and face.

During the first three days of November, on several occasions there was slight cyanosis. The baby regurgitated a number of times and cried considerably. There was no significant change in the heart action. During November 4 to 7 inclusive, the baby appeared well but the heart action remained the same. There was slight cyanosis only when the infant cried. She had been considerably more fretful and restless than is usual at this age.

On the morning of November 8, the child was no longer fretful and restless and had slept all night. On examination at 11:15 A.M. the heart rate was 144 a minute and the irregularity previously found on crying was no longer present. Subsequent examinations have revealed only normal heart action.

A systolic murmur, indefinite on examination of November 16 and 30, 1930, and January 3, 1931, was heard faintly but definitely on February 1 when the child was unusually quiet. This murmur was systolic, heard loudest over the base of the heart to the left of the sternum and faintly somewhat beyond the borders of the heart. The heart rate varied from 132 to 144 a minute with a normal rhythm. There was a slightly bluish tinge to the normal pallor about the mouth; the

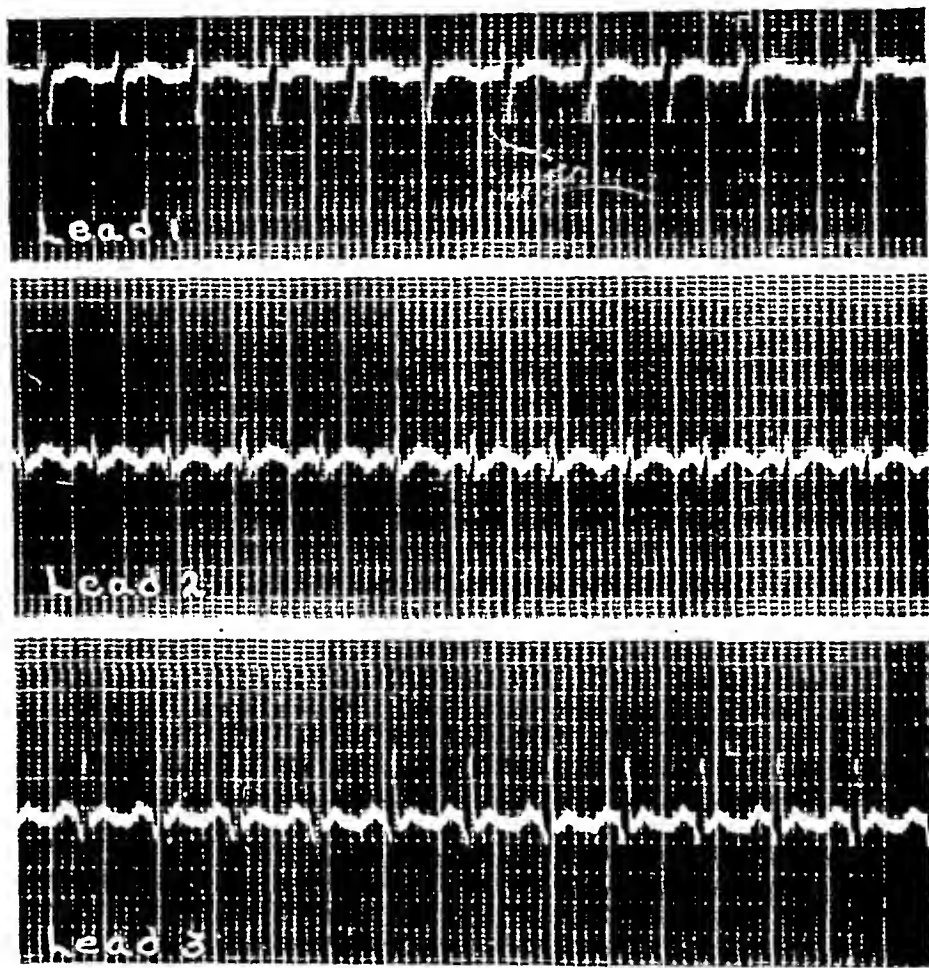


Fig. 3.—Electrocardiogram taken November 5, 1930. Flutter with 2-1 rhythm: 3-1 noted once in Lead 1.

cheeks were somewhat flushed and the color of the skin was good elsewhere. There was no cyanosis when the child cried.

X-ray examination on the afternoon of October 29, 1930, showed during inspiration, an upper mediastinal shadow of about 70 per cent of the width of the heart shadow. Dr. James T. Case, from roentgenologic studies, was of the opinion that there was an enlarged heart and thymus.

X-ray treatment for the thymus was given by anterior exposure on October 30, and by posterior exposure on October 31, and by both anterior and posterior exposures on November 28. Fluoroscopic examination of the heart on November 7 gave little additional information except to confirm the rapid heart beat. X-ray

examinations on November 8 and 28, 1930, and January 31, 1931, showed no definite evidence of enlargement of the thymus. The heart apparently was a little larger than normal.

When last examined, on March 8, 1931, the infant weighed 18 lb. 4½ ounces and was doing well. The heart action was normal. A slight systolic murmur was heard with difficulty. There was no cardiac irregularity and no cyanosis with crying.

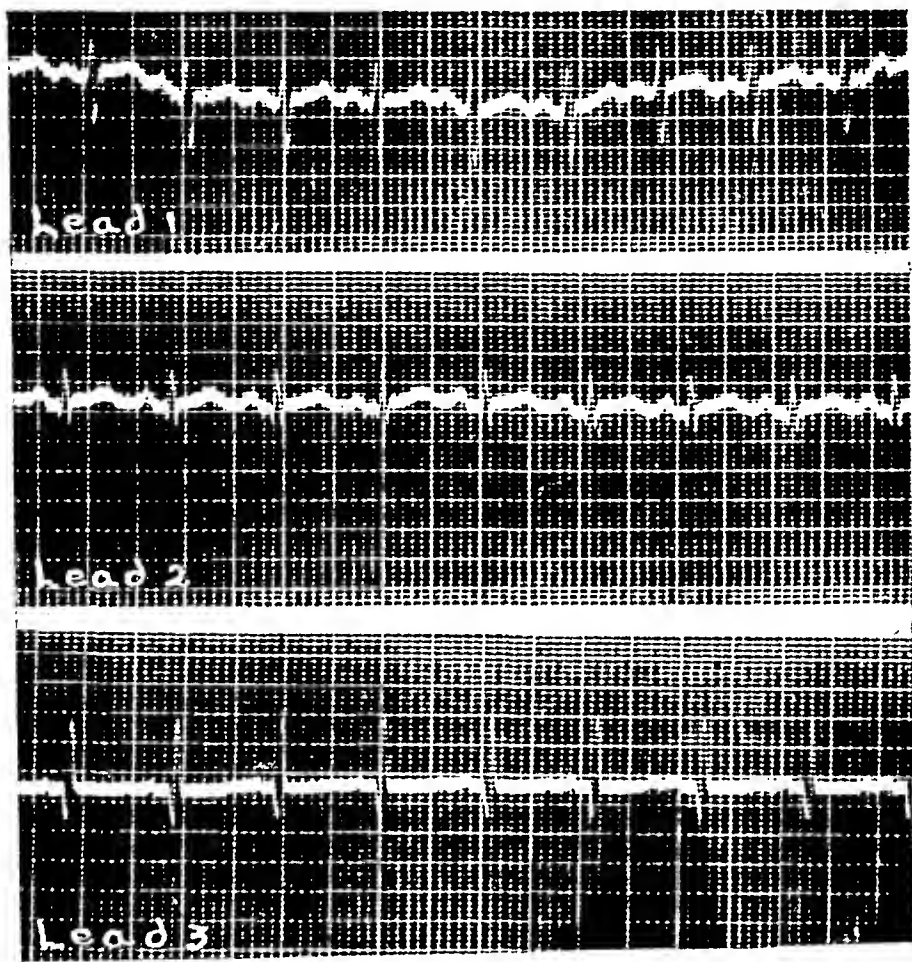


Fig. 4.—Electrocardiogram taken November 8, 1930. Normal mechanism. Rate 142.

SUMMARY

The important features in this case were: (1) a marked cardiac irregularity of a variable type which was noted *intra utero* during the last month of gestation; (2) after birth, a tachycardia with a rate of 180 to 192 beats a minute with periods of marked irregularity involving both rate and rhythm of the ventricular beat—the deeper respiratory movements, as with crying, markedly influenced these irregularities; (3) return to normal of the heart rate and rhythm on the tenth day after birth, with no recurrence of the abnormality; (4) establishment of the diagnosis of auricular flutter by electrocardiogram made about twenty-six and one-half hours after birth.

REFERENCES

1. Willius, Fredrick A., and Amberg, Samuel: Paroxysmal Tachycardia With Syncope Occurring in a Child, *Am. J. Dis. Child.* 38: 551, 1929.
2. Lewis, Thomas: *Lectures on the Heart*, New York, 1915, p. 116, Paul B. Hoeber.
3. Dressler, Wilhelm, and Löwy, Moritz: Ueber paroxysmale Tachykardia im Kindersalter, *Med. Klin.* 22: 1481, 1926.
4. de Bruin, M.: Paroxysmal Tachycardia in Infant, *Nederl. tijdschr. v. geneesk.* 74: 3415, 1930.
5. Doxiades: *Klin. Wehnschr.* 9: 454, 1930.

Department of Reviews and Abstracts

Selected Abstracts

Barcroft, Joseph, and Izquierdo, J. J.: The Relation of Temperature to the Pulse Rate of the Frog. *J. Physiol.* 71: 145, 1931.

The object of the present paper was by a comparative study of the temperature coefficients of the hearts of certain cold and warm blooded animals to gain further knowledge of the point at which the nervous system commences to dominate the response of pulse rate to temperature and, if possible, to ascertain the nature of the nervous control if such were found to exist. It deals with the effect of temperature on the pulse rate of the frog.

The excised frog's heart studied in winter time usually gives a linear relationship between the logarithm of the frequency of the sinus beat and the reciprocal of the absolute temperature between 5° and 20° C.

The value of Q_{10} varied in the minority of cases, as the temperature rose the frequency decreased as compared with the above relationship. In the intact frog in winter the results were irregular.

The excised heart of the frog in summer showed a different property. The frequency bore a nearly linear relation to the temperature. This was true also of the heart of the intact frog. The relation of the frequency to the temperature was little if at all, influenced by doses of atropine of the strength which just sufficed to block the vagus.

Barcroft, J., and Verzár, F.: The Effect of Exposure to Cold on the Pulse Rate and Respiration of Man. *J. Physiol.* 71: 373, 1931.

Apart from spasmodic rises in the pulse rate associated with shivering, the pulse rate in man falls with fall of body temperature. The spasmodic rises associated with shivering may amount to 40 per cent of the original pulse rate.

The respiration shows marked summation of inspiratory movements during the rigors which had very deep and sustained inspirations. The oxygen consumption increases during the shivering fits by as much as 75 per cent of its value during rest.

Patten, Bradley M.: The Closure of the Foramen Ovale. *Am. J. Anat.* 48: 19, 1931.

The author has studied hearts of over one hundred and sixty infants, ranging from newborn to the second year of age with especial reference to conditions at the foramen ovale. The cases were consecutive in the sense that they included every workable case which could be examined at first hand during the past three years. As a result of this study, the following summary is presented.

The abandonment of the foramen ovale as an equalizing short cut between the right and the left atrium is not an abrupt but a gradual process. At the close of embryonic life the pulmonary circulation is of sufficient volume to care for oxygen intake and carbon-dioxide elimination, so that there is no necessity of

assuming any revolutionary change in the course of blood through the heart at the instant of birth. Under the influence of the functional activity of the lungs, the pulmonary flow undergoes a smooth steady rise during the first few weeks after birth. The progressive diminution in the bore of the ductus arteriosus is concomitant and indicative of the postnatal increase in volume of the pulmonary circulation.

As the pulmonary circulation increases there is less compensatory flow through the foramen ovale from the right to the left atrium. This reduction in flow is evidenced anatomically by a parallel reduction in the fullness of the valvula foraminis ovalis, and the consequent diminution of the functional orifice to a progressively narrower slit between the valvula and the septum. This first phase in the closure of the foramen ovale occupies approximately the first postnatal month during which time the pulmonary return is mounting to equivalence with the right atrial intake. Although a probe can still be passed freely behind the valvula, the foramen ovale may be regarded as functionally closed when this new intracardiac balance has been attained and the valvula lies tightly against the septum.

Then follows a period of six to eight months in which the connective tissue of the valvula increases from 600 to 700 per cent. Probe patency still persists but the size of the slit through which a probe may be passed progressively diminishes and the resistance to its passage increases with the increase in the thickness of the valvula. This second phase in the closure of the foramen ovale with its characteristic histological alteration is essentially the conversion of an originally movable flap-like valve into a fixed septal structure.

Finally, coming leisurely in the wake of functional abandonment and as a culmination of the period of connective-tissue proliferation, is the adhesion of the valvula to become an integral part of the interatrial septum. There is great individual variability in the age at which this final step in the obliteration of the foramen ovale occurs. A usual range rather than a specific time of final anatomical closure is all that can be specified. Substantiated cases of complete fibrous adhesion of the valvula to the septum under three months are exceedingly rare. The usual time of complete anatomical closure appears to be not earlier than the last third of the first year after birth and is frequently much later.

Mere failure of the completion of the fibrous union of the valvula with the septum should be sharply distinguished from the frankly abnormal conditions in which the foramen ovale remains inadequately guarded. Incomplete adhesion with "probe patency" is so common that it must be regarded as a variant of the normal rather than as an abnormality. Approximately 25 per cent of all adult hearts show it in some degree. As long as the valvula foraminis ovalis adequately overlaps the limbus fossae ovalis, probe patency is no functional handicap to an otherwise normal individual.

Borman, Milton C., and Meek, Walter J.: IV. Coronary Sinus Rhythm. Rhythm Subsequent to Destruction by Radon of the Sino-Auricular Nodes in Dogs. *Arch. Int. Med.* 47: 957, 1931.

The authors in this study have tried to determine the exact site of the initiation of the cardiac impulse in dogs in which complete destruction of the sino-auricular nodes had been produced by radon. Twenty-one animals were studied. The previous observation that the nodal tissue of the coronary sinus apparently acts as a reserve mechanism, as a pacemaker under conditions of experimental destruction of the sino-auricular node is corroborated.

Evidence is presented that suggests that a coronary sinus rhythm cannot be differentiated from a sino-auricular rhythm by means of an electrocardiogram.

If the sino-auricular node is destroyed gradually by radon, the nodal tissue of the coronary sinus assumes the function of pacemaker. It is probable that when the

sino-auricular node is rendered functionless by disease the nodal tissue of the coronary sinus acts as pacemaker. Permanent nodal rhythm cannot be produced by destroying the sino-auricular node with radon.

The electrocardiographic changes in dogs following the destruction of the sino-auricular nodes by radon are: temporary reduction of the P-R interval which later becomes normal, slightly greater or slightly less than normal; decreased cardiac vagal tone; partial and complete sino-auricular block; partial and complete auriculo-ventricular block; nodal rhythm; coronary sinus rhythm; inverted T² and T³ and premature ventricular beats.

Izquierdo, Jose Joaquin: Experimental Evidence of the Controlling Action of the Aortic and Carotid Sinus Nerves Upon the Rises of General Blood Pressure. *Arch. Latino Amer. de Card. y Hemat.* 1: 193, 1931.

Comparison of the blood pressure curves obtained by stimulating the peripheral end of the splanchnic nerves by a constant cardiac stimulus under similar conditions, first with the two sets of aortic and carotid sinus nerves intact and then with these nerves partially or totally eliminated, was made in connection both with their maximal height, measured in mm. Hg, and with their form, specially the variations of the "step" or "dip" which occurs shortly after the beginning of the rise. The following results were obtained:

1. In the normal condition, the height reached by the splanchnic pressure curve is notably reduced by the action of the aortic and carotid sinus nerves, particularly the latter.

2. The typical and constant feature in the normal splanchnic pressure curve is related to the activities of the aortic and carotid sinus nerves, particularly the latter.

3. The two carotid sinus nerves and the two aortic nerves alone, are capable of exerting the same inhibiting effect upon the height and of producing the "dip" in the splanchnic pressure curve. Of the two pairs of nerves, the sinus nerves are those which exert the more important inhibitory effect.

4. When a single carotid sinus nerve is left active its effects upon the height and form of the splanchnic pressure curve are often considerable.

5. Tying off of both adrenals at the beginning of the experiment or after partial or total suppression of the aortic and carotid sinus nerves does not modify the results in the rabbit, the hare and the dog. But in the cat the "dip" more frequently disappears after the ipsilateral gland is tied off.

6. These two variations, namely in the height and "dip" in the curve are due to reflexes originating in the blood pressure receptors in the aortic and carotid sinus walls.

7. Both series of changes are compatible with the view that the rise of blood pressure produced by stimulation of the splanchnic nerve represents the balance between two factors working in the opposite direction, (2) the direct vaso-pressor effect (vasoconstriction in the splanchnic area), and "b" the indirect vaso-depressor effect (aortic and more especially carotid sinus reflexes) evoked by the rise of blood pressure.

Chillingworth, Felix P., Haskins, Frank E., and Casey, Gertrude U.: Assay of Tinctures of Digitalis. *Jour. Lab. & Clin. Med.* 16: 850, 1931.

The object of this survey was to determine to what extent tincture of digitalis as dispensed in representative drug stores of metropolitan Boston conformed in strength to the standard laid down as official in the United States Pharmacopeia. Although this is strictly speaking a local survey, the results are none the less of general interest owing to the fact that more than seventy-five per cent of the

tinctures assayed are the products of commercial pharmaceutical houses whose tinctures of digitalis are depended upon by practiced physicians throughout the country.

Eleven per cent of the tinctures assayed were above the U. S. P. requirements. In cases where massive doses are indicated, such over strength is especially dangerous. This percentage could not be explained by frog seasonal variation.

The evidence offered by this survey indicates that the variation in potency found in the tinctures varied less than that showed by other similar surveys. The authors believe that further improvement will take place when all manufacturers market their tinctures in sealed one-ounce bottles giving an expiration date.

Powers, John H., Pilcher, Cobb, and Bowie, Morris A.: Some Observations on the Circulation in Experimental Mitral Stenosis. Am. J. Physiol. 97: 405, 1931.

The purpose of this report is to present observations on the cardiac output of 5 dogs with experimental mitral stenosis. Since the animals had been utilized previously for some work on the blood volume of normal dogs, these studies were repeated after the development of mitral stenosis and are included. Alterations in cardiac size as demonstrated by roentgenological examination are also recorded.

The present consensus of opinion concerning heart disease in general favors the premise that the cardiac output per minute is decreased in proportion to the extent of cardiac damage. Experimental evidence to support this contention, however is extremely fragmentary and is not sustained by the results of these investigations.

The cardiac output of 4 of the animals ranged between 104 c.c. and 230 c.c. per kilogram per minute; the average was 170 c.c. These figures are within the range of normal. The output of the fifth animal was distinctly elevated being 323 c.c. per kilogram per minute.

The basal pulse rate was increased in four instances and normal in the fifth. The blood pressure was elevated in only one case. An increase in the percentage of red blood cells occurred at the expense of the plasma. No significant changes were observed in the electrocardiographic tracings. Observations on the control animal showed no variations from the normal.

The size of the heart as determined by the roentgen shadow showed a progressive enlargement in all five dogs.

Katz, L. N., and Wallace, A. W.: The Role of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram. Am. J. M. Sc. 181: 836, 1931.

The three cases reported indicate that acute myocardial ischemia depends not only on coronary occlusion and pericardial effusion but also on the competence of the heart and its dilatation. They also illustrate some of the errors liable to creep into the interpretation of the significance of the so-called "coronary R-T deformities." These observations substantiate the findings that coronary occlusions can be produced in normal animals without changing the R-T segment of the electrocardiogram. It was observed that such changes in the R-T segment ensue when the myocardium becomes incompetent.

Hurxthal, Lewis M.: The Clinical Significance of Abnormalities of the Electrocardiographic Complexes. New England J. Med. 205: 95, 1931.

The author describes in abstract form the usual interpretations passed on abnormalities of the various complexes of the electrocardiogram. Suitable electrocardiograms are published to illustrate the various points mentioned.

Drake, E. H.: *The Use of the Electrocardiograph in the Study of Cardiac Arrhythmias, Bradycardia and Tachycardia.* New England J. Med. 205: 92, 1931.

The author reviews briefly the important points observed in electrocardiograms from patients with these cardiac disturbances of mechanism.

Faulkner, James M.: *Methods of Electrocardiography and the Normal Electrocardiogram.* New England J. Med. 205: 88, 1931.

This brief presentation of the principles underlying electrocardiography and the description of the string galvanometer and the normal electrocardiogram gives a good idea of this field of physical examination. The brevity and clearness of the article makes it of value to beginners in the subject.

Sproull, John: *Roentgen Study of the Thoracic Aorta.* New England J. Med. 205: 83, 1931.

The author describes the findings of the heart and great vessels on roentgen examination and then briefly summarizes the common conditions producing changes in the aorta and their characteristic attendant roentgen changes.

Sosman, Merrill: *Roentgen Study of the Heart.* New England J. Med. 205: 80, 1931.

The author as a roentgenologist states that it is possible to assist in cardiac study in three ways: (1) by determining the exact size and shape of the heart and by making permanent records for future comparison; (2) by obtaining an idea through fluoroscopic examination as to the character of the heart beat and the condition of the myocardium; (3) by identifying isolated conditions such as aneurysm, calcified pericardium, Hodgkins disease and other mediastinal tumors.

Rösler, Hugo: *Methods of Cardiovascular Study by the Roentgen Ray.* New England J. Med. 205: 77, 1931.

The chief value of cardiovascular x-ray examination is in the case of the following conditions: (1) emphysema, thick or deformed chests and other thoracic diseases; (2) dilatation of the left auricle; (3) calcification and dilatation of the descending aorta; (4) thickening and calcification of the pericardium; (5) malformations; (6) diseases of the pulmonary arteries; (7) lung stasis in cardiac decompensation; (8) luetic aortitis.

The author describes the usual method employed in undertaking x-ray examination. Particular emphasis is placed on the value of fluoroscopic methods for observing the motion of the heart. Orthodiagrams and teleroentgenograms are also described. Mention is made of the value of plates made in oblique positions of the chest. Mention is also made of the use of barium mixtures for studying the relationship of the esophagus, aorta and pericardium.

Grimes, Eli: *Effect of Intrathoracic Pressure on Arterial Tension.* Arch. Int. Med. 47: 876, 1931.

The author states that if a person shuts off the outlet of air by closing the larynx or nose and lips and makes a forced expiratory effort the intrathoracic pressure rises and the blood cannot flow into the chest; hence the right side of the heart does not fill, the blood is soon pumped out of the lungs and the left ventricle likewise becomes empty, arterial circulation is momentarily suspended and the systolic blood pressure falls to zero. After the systolic pressure has fallen, respira-

tion is resumed and the systolic pressure rises from 50 to 150 above the patient's normal pressure. This rebound depends on the amount of blood, the elasticity of the arteries and the contractile force of the heart. Other conditions being constant the elevation in pressure is in inverse ratio to the elasticity of the arteries, therefore, the respiratory rebound is a measure of the elasticity of the arteries.

A high respiratory rebound is the first indication of oncoming hypertension and of arterial fibrosis with or without high pressure. A person showing a high rebound should be intensively studied for syphilis and nephritis. The test does not indicate the integrity of the heart, measure its efficiency or foretell its failure.

De La Chapelle, Clarence E., and Graef, Irving: Acute Isolated Myocarditis.
Arch. Int. Med. 47: 942, 1931.

A case of so-called myocarditis of unknown etiology is reported. Clinical and necropsy observations are compared with those in previously recorded cases.

Progressive heart failure was the outstanding clinical feature. The embolic phenomena noted during life and the evidence for the same found at necropsy are particularly noteworthy and possibly give a clue to the onset and duration of the lesion. The cerebral accident about eight and one-half months before death, the healed infarct in the kidney and the probable pulmonary infarct about six weeks before death suggest that the intracardiac thrombi were present for some time. The heart weighed 600 grams and exhibited marked hypertrophy lending further support to the contention that the disease had existed for a period of months.

The diffuse and focal cellular infiltration consisting chiefly of lymphocytes, the new formation of blood vessels and connective tissue involving both the interstitium and the parenchyma, the well-marked deposits of organized connective tissue and the focal areas of necrosis account for the progressive circulatory failure. There were no vascular, perivascular or myocardial lesions suggestive of rheumatic infection and no Aschoff bodies were found. Electrocardiograms gave further evidence of the extensive distribution of the lesion.

Willius, Fredrick A.: The Heart in Old Age. A Study of 700 Patients Seventy-Five Years of Age and Older. *Am. J. M. Sc.* 182: 1, 1931.

This study is based on 700 patients 75 years of age and older who were carefully investigated at The Mayo Clinic from August, 1914, to January, 1930, with special reference to the cardiovascular system. This group represented an incidence of 1.1 per cent of persons who had undergone electrocardiographic examinations.

The ages of the patients ranged from 75 to 96 years. Forty-seven per cent of the patients were aged 75 and 76 years. The numbers in the various groups diminished progressively with advance in age; only 0.5 per cent were between the ages of 91 and 96. The ratio of the sexes was 5 men and 1 woman. Seventy and three-tenths per cent of the patients had systolic blood pressure of 140 mm. or more; only 9.7 per cent had systolic blood pressure of 200 mm. or more. The mean blood pressure ranged from 109 to 127.8 mm. The diastolic pressure of 110 mm. or more occurred in 107 cases. Pulse pressure of 60 mm. or more occurred in 69.6 per cent of cases and readings of 90 mm. or more in 20.7 per cent. It is evident from this study that hypertension is the rule in aged patients. There were 315 patients without clinical evidence of heart disease as opposed to 385 patients with clinical evidence of heart disease.

From this study of aged patients, one gleans the impression that the majority of persons even in the presence of evident heart disease, possess hearts of unusual quality. This impression becomes strengthened by the fact that only 85 patients had congestive heart failure. The heart impaired or unimpaired by disease that permits continuation of life to and beyond the seventy-fifth year is an organ of unusual quality.

Reinhart, Alfred S.: *Evolution of the Clinical Concept of Rheumatic Fever*. New England J. Med. 204: 1194, 1931.

The author traces the history of rheumatism through the ages and stresses that portion of it which depicts successive recognition of the protean manifestations of rheumatic fever from the point of view of the historical evolution of the present concept of the disease. References to the literature are frequent and many important historical contributions are listed, particularly the early contributions describing the unusual features of rheumatic fever.

The author believes that the extra articular and the extra cardiac manifestations of rheumatism have been receiving increasing attention and recognition, and that the apparent clinical rarity of some of these manifestations will become less marked as clinicians pay more especial attention to and look more carefully for their presence. He points out the important fact that there is a changing conception of the disease from a local affection to a generalized affliction.

Boas, Ernst P.: *Rheumatic Fever in Adult Porto Rican Immigrants*. Am. J. M. Sc. 182: 25, 1931.

The author has studied native Porto Ricans admitted to Mount Sinai Hospital with rheumatic fever. Nine of the cases were severe and were similar to the type usually seen in childhood. This observation suggested that the increased virulence of the disease might be explained by the absence of rheumatic infection in Porto Rico results in a greater susceptibility of Porto Ricans on exposure to the disease in the United States where rheumatic fever is endemic.

Registration of deaths shows that rheumatic fever and rheumatic heart disease are very rare in Porto Rico. From the records available, the author has determined that rheumatic infection is not very common among Porto Ricans who have immigrated to New York City.

Clawson, B. J.: *Experiments Relative to a Possible Basis for Vaccine Therapy in Acute Rheumatic Fever*. J. Infect. Dis. 49: 90, 1931.

The purpose of these experiments was to learn whether or not there may be an experimental basis for vaccine therapy in patients having acute rheumatic fever. Starting with the fact that there is a similarity between the state of allergy toward streptococci in patients with acute rheumatic fever and that in animals made hypersensitive to streptococci experimentally and with the fact that hypersensitized animals can be desensitized, the author attempted to desensitize hypersensitive animals by means of intravenous vaccination.

The development or the non-development of subcutaneous nodules was used in the detection of hypersensitiveness or desensitization respectively. If the development of these nodules can be prevented in animals it was considered possible that by a similar method to desensitize patients having acute rheumatic fever and to prevent further development of lesions.

It was found that rabbits made hypersensitive to streptococci can be desensitized by such intravenous administration of a streptococcal vaccine. Injections of doses of streptococci that produced marked lesion in hypersensitive animals have little or no effect on vaccinated hypersensitive animals. This protective phenomenon is not strictly type specific but seems probably species specific. Protection is uniformly associated with a high titer of agglutination while hypersensitiveness is not. From experiments reported in this paper the possibility of the use of intravenous vaccine treatment in patients with acute rheumatic fever is suggested.

Wilson, May G., and Swift, Homer F.: Intravenous Vaccination with Hemolytic Streptococci. *Am. J. Dis. Child.* 42: 42, 1931.

The present investigation covers a period of observation of four years on a total of one hundred and seventy-two children attending the Heart Clinic of the New York Nursery and Child's Hospital. Approximately one-half of the children received intravenous vaccination and the remaining number, a comparable group, were observed as control series. The vaccine used was prepared at the hospital of the Rockefeller Institute. It consisted of a heat-killed culture of hemolytic streptococcus strain Q 33 suspended in 0.5 per cent phenolized physiologic solution of sodium chloride so that 1 c.c. represented the required dose. The first injection consisted of 250,000 micro-organisms and each subsequent weekly injection contained double that of the preceding one until the maximum of 10,000,000 was reached and this dose was repeated until a total of from nine to twelve treatments had been given.

The incidence of recurrence and manifestations of activity in both groups was comparable during two years, 1927-28 before vaccination was given. The yearly incidence of recurrence in the treated group was less than in the control group during the two years 1929-30 after treatment. Forty-five per cent of the treated children as compared with 18 per cent of the controls were free from recurrence for periods of from sixteen months to two years after treatment.

The causal relation of intravenous vaccination with hemolytic streptococcal vaccine to the diminished incidence of recurrence observed is discussed. Final judgment as to the causal relation must await the results of further investigation. It would seem best at the present time to restrict the therapeutic application of intravenous vaccination in rheumatic children to control investigation.

Sellirk, Theodore K., and Mitchell, A. Graeme: Evaluation of the Results of Tonsillectomy and Adenoidotomy. *Am. J. Dis. Child.* 42: 9, 1931.

This study follows the methods commonly employed by other investigators in studying the effects of tonsillectomy and adenoidotomy and includes one hundred and thirty children who had had operation. The authors analyze the physical findings and symptoms in this group of children subsequent to operation as compared with those previous to operation. In this series there were ten cases of rheumatic infection. The incidence of attacks of joint pains following operation is not stated in this article. In general, it was noted in this study that three years after tonsillectomy and adenoidotomy there was a lessened incidence of colds, nasal obstruction and sore throat while sinus infection, headache and growing pains were increased in frequency.

This paper is concerned chiefly with the statement of the difficulties surrounding the whole problem. The authors feel that this study of the after results of the operation has added to their doubts of the possibility of analyzing satisfactorily their own personal observations and has increased their skepticism of the conclusions drawn from many of the studies made by others. They believe that no attention, or too little attention has been paid to certain modifying factors, principally age, sex, race, heredity, financial class, season, effect of adenoidotomy alone, length of observation after operation, source from which the history and other data are obtained, incidence of tonsillectomy in the community at large and the suitability of the control group.

They state that many of the symptoms and conditions popularly supposed to be associated etiologically with diseased tonsils are those in which the natural course and incidence regardless of the tonsillectomy are not known. It would seem that the conclusions drawn from some of the studies which are widely quoted as showing the effects of tonsillectomy are decidedly open to question because of failure to consider other factors in evaluating the results.

Chapin, Laurence D.: *The Treatment of Heart Disease in General Practice*. New England J. Med. 205: 220, 1931.

The author relates briefly his opinions regarding the general aspects of various forms of heart disease as formed from general practice. His own personal experience with his family led him to a keen interest in this subject which he has followed for a great many years. The material is general in nature but is interesting to record.

Ramsay, Robert Ewart, and Crumrine, R. M.: *Coronary Thrombosis, in an Infant Aged Four Months*. Am. J. Dis. Child. 42: 107, 1931.

Autopsy on the body of a girl aged four months eight days revealed coronary thrombosis. A photograph of the heart shows a thrombus in the vessel cut transversely in the distal portion of the vessel distended by the thrombus in situ. The wall of the left ventricle showed dimpling due to thinning of the muscle. A detailed description of the pathologic process appears in this report. The infant had been slightly ill with symptoms suggestive of some hidden infection. Following apparent recovery she became suddenly ill with distress and difficult breathing; death occurred in a few hours.

Microscopic examination is in agreement with the summary of the gross examination and confirms the supposition that the original lesion of the coronary artery was of an infectious nature, probably bacterial embolus. The embolus grew in the artery and produced increasing thrombosis until the occlusion was complete.

Schwab, Edward H., and Sanders, C. B.: *Aortic Aneurysm Rupturing Into the Conus Arteriosus of the Right Ventricle*. Am. J. M. Sc. 182: 208, 1931.

A case of acquired aneurysm of the ascending aorta with rupture into the conus arteriosus of the right ventricle is reported. The resulting physical signs simulate very closely those of congenital heart disease.

Reid, William D.: *Congenital Dextrocardia; An Apparently Unique Case*. New England J. Med. 205: 151, 1931.

A case is reported of congenital dextrocardia of the nonmirror image type and acquired stenosis of the aortic valve. A full report, including the findings on post-mortem examination is included. It is interesting that the roentgen plate confirmed the clinical diagnosis of dextrocardia and by means of the fluoroscope it was disclosed that the cardiac apex was located in its normal relationship to the remainder of the heart, rather than to the right as in the mirror image type of dextrocardia. The case appears to be unusual also in that this type of congenital dextrocardia occurred without other congenital malformations of the heart.

Arnett, John H., and Long, Charles-Francis: *A Case of Congenital Stenosis of the Pulmonary Valve With Late Onset of Cyanosis*. Am. J. M. Sc. 182: 212, 1931.

A case of a patient with simple congenital pulmonary stenosis is presented, who after an exceeding athletic career gradually developed localized areas of cyanosis believed to be due to the stasis of blood within dilated minute blood vessels of the skin. Physical examination established a diagnosis of heart disease suggestive of pulmonary stenosis. This was confirmed at autopsy. Death in this case came at the age of thirty-three as a result of carcinoma of the pancreas. Attention is called to the fact that cyanosis due to vascular stasis is not uncommon in congenital cardiac disease and occurs in other conditions as well.

Ayman, David: **Essential Hypertension. The Diastolic Blood Pressure: Its Variability.** *Arch. Int. Med.* 48: 89, 1931.

In seventy-six unselected, untreated patients with essential hypertension, the diastolic blood pressure was found to fluctuate widely during periods of observation extending in the individual case up to one and one-half years. The series of patients included those with advanced essential hypertension as well as those with milder forms. It was found that in all cases the diastolic blood pressure fluctuated over a wide range. The percentage of fluctuation was found to be as great as that of the systolic blood pressure. There was no appreciable difference between patients with severe hypertension and those with milder forms.

The degree of fluctuation was found to vary to a certain extent with the number of observations made on the patient: the more frequent the observations, the greater the fluctuation recorded. The lowering effect on the diastolic blood pressure of sitting in a quiet room also seems definite and conversely, the elevating effect of excitement. There were no patients who had a fixed nonfluctuating hypertension.

Sanders, Audley O.: **Postural Hypotension.** *Am. J. M. Sc.* 182: 217, 1931.

In this case the symptoms of anemia of the brain came regularly with the upright position and promptly disappeared with the lowering of the head to body level. These phenomena recurred quite constantly over a period of years. It is of special interest in this case that the symptoms began on a definite date with a definite experience. It seemed reasonable to assume that a lesion of the autonomic system was incurred at that particular time.

McIlroy, Dame Louise, and Rendel, Olive: **The Problem of the Damaged Heart in Obstetrical Practice.** *J. Obst. & Gynec. Brit. Emp.* 38: 7, 1931.

The present communication is based on a series of 200 cases of heart disease in 226 pregnancies which have been investigated during the last six years. The numbers occurring in the different classes were as follows:

| | PRIMIGRAVIDAE | MULTIPARAE | TOTAL |
|--------------|---------------|------------|-------|
| Class I | 35 | 23 | 58 |
| Class II (a) | 48 | 47 | 95 |
| Class II (b) | 14 | 49 | 63 |
| Class III | 2 | 8 | 10 |
| | — | — | — |
| | 99 | 127 | 226 |

The enormous relative increase of multiparae in Group II (b) emphasizes the fact that multiple pregnancies tend to lower the cardiac efficiency permanently. The actual anatomical lesion found appears to have very little bearing on the prognosis except in so far as the severer lesions obviously produce a greater mechanical strain.

The efficient treatment of heart disease complicated by pregnancy depends upon early antenatal examination and the cooperation between the obstetrician and the cardiologist. The establishment of antenatal cardiac clinic is an essential part of an obstetrical hospital.

Skilled medical treatment has diminished to a considerable extent indication for the artificial termination of pregnancy. Heart disease of moderate severity does not preclude successful pregnancy provided that efficient care throughout antenatal period, delivery and post natal period is exercised. The chief factor is rest. One must, however, bear in mind that every pregnancy is a big strain on the damaged heart and that even in the milder cases, recovery of its former functional efficiency will take time and in spite of every attention may be incomplete. In

severer cases, there is a distinct possibility of transferring a patient into a heart category of lower grade.

It is more important to prevent a pregnancy taking place than to terminate it, since termination is only likely to be successful if performed in the early stages of pregnancy.

Rest, diet and general hygiene are of greater importance than drugs in the successful management of heart disease complicated by pregnancy. Labor should be made as easy as possible by the employment of sedatives and intermittent anesthesia. Delivery by forceps may be indicated in order to shorten the second stage in severe cases.

Yater, Wallace M., and Trehwella, Arthur P.: The Case For and Against the Operative Treatment of Angina Pectoris. Am. J. M. Sc. 182: 35, 1931.

The authors report a case of angina pectoris which had been severe enough to warrant the use of surgical procedure. They have also studied from the literature a group of 138 cases on whom neurectomy had been done for angina pectoris. They believe that the operative treatment for angina pectoris at present should be performed only in selected cases and by neurosurgeons who wish to study carefully the anatomy and physiology of the innervation of the heart and aorta and the reasons for the postoperative complications.

Levy, Robert L., and Moore, Richmond L.: Paravertebral Injections of Alcohol for the Relief of Cardiac Pain. Arch. Int. Med. 48: 145, 1931.

The authors have reviewed the literature, reporting fifty-seven cases and have described their observations on nine patients treated by them with paravertebral injections of alcohol for relief of cardiac pain. The technic of injection as described is relatively simple but the authors believe it requires skill acquired by experiments on a cadaver.

They believe that there is relief of pain in a large number of patients and in one case, there was complete relief for sixteen months. There were no unfortunate results following the injection; occasional discomfort, fever, etc., may be noted. Two patients had effusion into the left pleural cavity following the injections.

Paravertebral injection of alcohol offers a reasonably good hope of some relief to patients with paroxysmal cardiac pain. Final judgment as to its value and limitations must be reserved until more cases have been observed over longer periods of time. For the present, it should be tried only after carefully planned medical treatment has failed to alleviate intense suffering. The method has a sound physiologic basis and is less dangerous than cervical sympathectomy. The basic pathologic condition in these patients is entirely unaltered, therefore patients in whom pain has served as a danger signal of overexertion should be warned, if relieved from attacks, against exceeding the functional capacity of the heart.

Book Reviews

HEART DISEASE. By Paul Dudley White. The Macmillan Company, New York, 1931. Pp. 931, 119 illustrations.

The author states that the need for a clear, concise and comprehensive presentation of the diagnosis and treatment of heart disease in the light of our present knowledge caused him to write this book. It is intended chiefly for the use of students and practitioners. The book has been divided into four parts: the first deals with the examination of the patient and the analysis of his symptoms and signs; the second discusses the etiological types and causes of heart disease; the third deals with the structural changes present in the heart and great vessels; the fourth takes up disorders of function.

Not so many years ago the heart might justly have been considered a narrow field for specialization. Newer methods and rapid extension of knowledge have already made it difficult to keep fully abreast solely with the clinical aspects of the subject. Consequently in a book of this type in which there is great need for selection of material and condensation demanding the exercise of knowledge and judgment, one expects to find high lights and shadows. To the credit of the author be it said that the high lights are many, the shadows few and rarely dense. The book shows clearly the results of careful effort in its preparation. It has been shorn of most of the traditional error and deadwood that usually cling to textbooks.

The most valuable discussion in the book is that which deals with the patient's history. The art of history taking in these days of standardized forms is in danger, unless there are to be found those who will resolutely oppose the tendency to regard tabulation of symptoms, valuable though these may be for statistical purposes, as a satisfactory history. The author has not permitted himself to be misled by the glamour of newer methods of study into minimizing the value of the history. On the contrary he recognizes the fact that the more one knows of heart disease, the better the history he should be able to obtain.

In the section on physical examination, the part entitled "Examination other than Cardiae" might have been further elaborated with profit. The least satisfactory presentation in the book is that dealing with auscultation. This is perhaps not the fault of the author; advance in this field seems to have stopped with Potain. Unfortunately there have been reproduced many of the sound tracings published by Lewis apparently without realization, at least without mention, of the

limitations of these tracings. There are numerous positive statements in this section which the reviewer believes to be either actually erroneous or subject to qualification.

The text of the chapter on the highly important subject of cardiovascular roentgenology is not quite up to the general standard of the book, although the illustrations are excellent. The author regards the cardio-thoracic ratio as the most useful single calculation of heart size. He barely mentions the area of the antero-posterior silhouette although this calculation is probably far more significant than that of the cardio-thoracic ratio. The importance of oblique views is appreciated but, curiously, nothing is said of the lateral view.

The discussion of etiological factors is in some respects inadequate. This applies particularly to infections other than rheumatic fever and syphilis, and to a chapter designated "Other Etiological Factors and Relationships." The extreme importance of etiology warrants more complete presentation, even at the expense (if necessary) of other subjects.

The chapters on electrocardiography, abnormalities of cardiac mechanism, angina pectoris, neurocirculatory asthenia are particularly well done. The discussion of treatment seems remarkably sound. The author has apparently divested himself completely of therapeutic superstition.

A pleasing feature is the inclusion of extracts from papers of historical importance, thus adding greatly to the interest of the book and providing the reader with some of the background necessary to appreciate the present status of knowledge. It is to be hoped that these skillfully selected extracts will help to stimulate more widespread interest in the medical classics.

The bibliography is excellent. The author wisely refrains from cluttering the text with references. At the end of the book titles are arranged according to subject. Thus the reader has assembled for him a set of references which covers satisfactorily practically all subjects falling within the scope of the book.

The book should serve admirably either as a text or reference work for practitioners. It will repay careful study by all who are interested in diseases of the heart. It is too long for routine use by undergraduates, curricula being as they are, but it may be warmly recommended to students who are attracted to the study of heart disease.

C. C. W.

THE FACTOR OF INFECTION IN THE RHEUMATIC STATE. By Alvin F. Coburn. Williams and Wilkins Company, Baltimore. Pp. 288, fully illustrated, with 7 color plates.

This book is the published results of a study of the rheumatic state in its many phases. The work has been done principally at the Pres-

byterian Hospital in New York and with a small colony of rheumatic subjects in Porto Rico. The study has been essentially clinical in nature, dealing principally with the field of bacteriology and the observation of patients with rheumatic fever. The reviewer finds himself so fully in accord with the ideas expressed in the text and with the observations made on patients that it is difficult to do anything less than recommend the book in most enthusiastic terms.

The scope of the book deals with the impressions that exist at present concerning the rheumatic state. This term is used by the author to include that great mosaic of disease manifestations which in the past has been described under the title of "acute articular rheumatism" and which is now usually entitled "acute rheumatic fever." Except for bacteriological studies of the body tissues and blood, certain anatomical changes of material removed at necropsy and a few serological tests, the book is devoted almost exclusively to the description of clinical manifestations of this disease.

The outstanding feature of the text is the very large amount of clinical material presented in the form of brief case reports illustrating the many ideas expressed by the author. These case reports are interesting and show clearly what occurs in many patients. The case reports are inserted directly in the text. The scope of the book is necessarily limited to this field because, as the author states, this disease does not readily yield itself to any other means of investigation. While it is strongly suspected and probably accepted that the streptococcus is the etiological agent, yet it is difficult to recover the organism from the host, and as yet no suitable animal has been found which yields itself to experimentation. This feature of the rheumatic state, as is well known, makes it difficult to subject this disease to satisfactory scientific laboratory investigation. However, the author's method of handling the subject is a very good example of proper clinical scientific investigation.

It would be difficult to take up all the ideas expressed by the author for analysis. There are many important ones and only a few can be mentioned.

Chapter I deals with the rheumatic state. This description is clear and presents a very comprehensive idea of this protean disease, as it is understood at the present time.

Chapter II is devoted to the author's bacteriological studies on two important phases of the disease: (1) the incidence of a bacteremia; (2) an investigation of bacterial endocarditis and its association with the rheumatic state. In this study a bacteremia was only occasionally found in patients with the disease. In patients with high fever and other symptoms which suggested such a bacteremia it was possible to recover organisms occasionally, usually streptococci, from the circulating blood with careful cultural methods. However, a very large

number of patients showed sterile cultures. It is believed that bacterial endocarditis is a form of heart disease associated with some other injury in the heart and that while bacterial endocarditis may be superimposed on rheumatic carditis or may exist in the same patient at the same time, the two conditions are separate and distinct. These ideas are in accord with those generally held by other workers.

Chapters III and IV deal with some general impressions and observations of rheumatic disease as it appears on the Presbyterian Hospital Wards in New York. These observations are related to the annual and seasonal variations of the disease, its regional distribution, the question of the "rheumatic family" and other equally important features of the disease. It is important to note that the author found rheumatic manifestations among immigrants newly arrived from regions which are ordinarily free from rheumatic infection. It was observed that a group of rheumatic individuals taken from New York City to Porto Rico became relatively free of the disease after several weeks' residence in the tropical region and that their disease reappeared when they returned to New York.

Chapter V deals with observations on the upper respiratory bacterial flora in man and its relationship to the rheumatic state. This includes a study of the tonsils removed at operation as well as the cultural studies of the flora of the upper respiratory area. In Chapter VII the question of tonsillectomy in individuals with rheumatic fever is discussed. It is pointed out that recrudescence of the disease frequently follows such an operation. In this same chapter the relationship between scarlet fever and rheumatic fever is also discussed. The author believes that scarlet fever is related to the rheumatic process in some individuals who gave no clinical evidence of being stigmatized with the rheumatic state, and found that it appeared to be responsible for several recrudescences of the disease in others. All the facts collected during this study point to the importance of scarlet fever as a factor of infection in the rheumatic state.

Chapter VI deals with reactions of the skin to intracutaneous injection of bacterial nucleoproteins.

It is not the scope of this book to present the historical side of rheumatic fever; as stated above, it is principally concerned with the author's observations of the condition as it exists at the present time.

The bibliography includes all the important writings on the various phases of this subject and is exceptionally well selected.

The form of the book is excellent. It is well printed, the illustrations, including a frontispiece showing a composite picture of the disease, are unusually good and there are numerous helpful charts.

H. McC.

INDEX TO VOLUME VI

(An asterisk [*] after a page number indicates that the reference is an abstract and not an original article.)

A

- Alcohol, paravertebral injections of, for the relief of cardiac pain, 840*
- Allen, Ellery G., and Reifensstein, E. C., 274
- Amyl nitrite, effect of, on the size of the heart and the width of the aortic shadow as determined roentgenologically, 299*
- Anderson, Dorothy H., and Baily, F. R., 338
- Anderson, Marie C., 578*
- Andren, Thekla, Levine, S. A., and Homans, K., 430*
- Anemia, change in size of heart in, 517
- Aneurysm, aortic, rupturing into the cunus arteriosus of the right ventricle, 838*
- arteriovenous, between aorta and superior vena cava, 281
- surgical, the treatment of thoracic aneurysm by, 426
- of the thoracic aorta, 274
- Angina pectoris, case for and against operative treatment of, 840*
- comparison, with experimental temporary coronary occlusion, 580*
- electrocardiographic changes during brief attacks of, 579*
- inhalation treatment of, and intermittent claudication, 548
- in the young adult, 423
- observations on, 714*
- rôle of syphilis in the etiology of, 163
- Antopal, William, Gross, L., and Sacks, B., 575*
- Aorta, aneurysm of, 274
- arteriovenous between superior vena cava, 281
- coarctation of, dynamics of the circulation in, 718*
- fluoroscopic studies of heart and, in syphilis, 67
- localization of luetic virus in, 42
- roentgen study, 834*
- studies of, with reference to luetic aortitis, 77
- thoracic, unusual variation of the roentgen shadow of the elongated, 768

- Aortic valve, calcareous, 349
- insufficiency, syphilitic, 56
- differentiation of, from functional and other forms of, 107
- experimental, changes in ventricular size and in left ventricular discharge, 299*
- symptoms and clinical course, 86
- sclerosis of, clinical aspects of, 436*
- subclavian pulse in disease of, 778
- Aortitis, syphilitic, roentgenological diagnosis in, 59
- studies of the aorta in, 77
- with negative Wassermann reaction, 116
- Arnett, John H., and Long, Charles-Francis, 838*
- Arsenicals, use of, in treatment of cardiovascular syphilis, 142
- Arteriosclerosis, coronary, rôle of syphilis in etiology of, 163
- Arteritis, primary bacterial pulmonary, case of patent ductus arteriosus with, 555
- streptococcus viridans of pulmonary artery associated with patent ductus arteriosus and pulmonary stenosis, 584*
- Arthritis, chronic infectious, subcutaneous nodules in, 438*
- Ashman, Richard, and Herrmann, G., 375
- Auricle, anomaly of, 230
- contraction of, influence of, on first heart sound and radial pulse, 438*
- Ayman, David, 839*
- and Pratt, J. H., 716*

B

- Bacteria, tissue reaction in rabbits following intravenous injection of, 294*
- Bailey, F. R., and Anderson, D. H., 338
- Bain, C. W. C., and East, C. F. T., 445
- Baker, Benjamin M., Jr., and Carter, E. P., 715*
- Balboni, Gerardo M., Bland, E. F., and White, P. D., 585*
- Baldrich, C. W., and Fowler, W. M., 183
- Ball, David, 517
- Barcroft, J., and Izquierdo, J. J., 830*
- and Verzár, J., 830*
- Barium chloride in the Stokes-Adams syndrome of complete heart-block, 431*

- Barker, Paul S., Wilson, F. N., and MacLeod, A. G., 637
- Barnes, Arlie, R., Margolis, H. M., and Ziellenen, F. O., 349
- Batson, Oscar V., and Bellet, S., 206
- Baxter, W. S., and Cullinan, E. R., 420
- Bedford, D. Evan, and Parkinson, J., 579*
- Bellet, Samuel, and Batson, O. V., 206
- Beresford, E. H., and Earl, C. J. C., 578*
- Bismuth subnitrate in the treatment of arterial hypertension, 305*
- Blackford, L. Minor, and Hoppe, L. D., 718*
- and White, P. D., 333
- Bland, Edward F., Balboni, G. M., and White, P. D., 585*
- Hampton, A. O., and Sprague, H. B., 77
- Blood flow, velocity of circulatory response to thyrotoxicosis, 297*
- comparison of, in myxedema and thyrotoxicosis, 297*
- relation of changes in, and blood velocity to changes of posture, 437*
- oxygen and CO₂ of, from the internal jugular and other veins, 304*
- pressure, arterial, experimental evidence of the controlling action of the aortic and carotid sinus nerves upon the rise of, 832*
- diastolic, in essential hypertension, its variability, 839*
- vessel disease, peripheral, dermatherm in relation to, 683
- methods for estimating the degree of sympathetic vasoconstriction, 719*
- Blotner, Harry, 303*
- Blumgart, Herman L., Gargill, S. L., and Gilligan, D. R., 297*
- Lawrence, J. S., and Ernestene, A. C., 718*
- Boas, Ernst P., 788, 836*
- Bock, A. V., Dill, D. B., and Edwards, H. T., 437*
- Bogan, M. E., Hurxthal, L. M., and Menard, O. J., 575*
- Boots, R. H., and Dawson, M. H., 438*
- Borman, Milton C., and Meek, W. J., 831*
- Boswell, Clarence H., and Palmer, H. J., 717*
- Bowie, Morris A., Powers, J. H., and Pileher, C., 833*
- Brams, William A., and Gaberman, P., 804
- and Strauss, H. A., 299*
- Bramwell, Crichton, and Ellis, R., 714*
- Brown, George E., 298*
- Buffum, William P., 475*
- Byron, Charles S., and Wishnofsky, M., 717*
- C
- Calhoun, J. Alfred, and Harrison, T. R., 58*
- Cullen, G. E., Clark, G., and Harrison, T. R., 582*
- Pileher, C., Cullen, G. E., and Harrison, T. R., 296*
- Campbell, Maurice, and Parkinson, J., 578*
- Carr, James G., 30
- and Hines, L. E., 142
- and McClure, W. B., 824
- Carter, Edward P., and Baker, B. M., Jr., 715*
- Casey, Gertrude U., Chillingworth, F. P., and Haskins, F. E., 832*
- Cassio, P., and Padilla, T., 321
- Chapin, Laurence D., 838*
- Chillingworth, Felix P., Haskins, F. E., and Casey, G. U., 832*
- Circulation changes following birth, 192
- Clark, Gurney, Pileher, C., and Harrison, T. R., 296*
- Claudication, intermittent, inhalation treatment of, and angina pectoris, 548
- Clawson, B. J., 294*, 836*
- Coburn, Alvin F., 842
- Cold, effect of exposure to, on the pulse rate and respiration of man, 830*
- Cooksey, Warren B., and Freund, H. A., 608
- Cookson, Harold, 293*
- Coronary artery, involvement of, in rheumatic fever, 576*
- in health and disease, 589
- disease in diabetes mellitus, 303*
- occlusion (book review), 721
- acute, appearance time of T-wave changes in electrocardiogram following, 304*
- experimental temporary, comparison with angina pectoris, 580*
- heart sound failure in, a phonocardiographic study, 577*
- mild forms, 597*
- serial electrocardiographic studies in, 608
- with complete heart-block and relative ventricular tachycardia, 820
- rupture, hemopericardium, 713*
- thrombosis, in an infant aged four months, 838*
- Cotton, Thomas F., 576*
- Cowan, John, 714*
- Crummer, LeRoy, 308
- Crumrine, R. M., and Ramsay, R. E., 838*
- Cullen, Glenn E., and Harrison, T. R., 582*

- Cullen, Glenn E., Calhoun, J. A., Clark, G., and Harrison, T. R., 582*
 Pilcher, C., and Harrison, T. R., 296*
 Cullinan, E. R., and Baxter, W. S., 420

D

- Danglade, James H., and Moore, J. E., 148
 Dawson, M. H., and Boots, R. H., 438*
 Death, mechanism of, of human heart as recorded in the electrocardiogram, 743
 DeGraff, Arthur C., and Gold, H., 301* and Strax, P., 807
 De La Chapelle, Clarence E., and Graef, I., 835*
 Derick, C. L., Hitchcock, C. H., and Swift, H. F., 295*
 Dextrocardia, congenital, an apparently unique case of, 838*
 Diabetes mellitus, coronary disease in, 303*
 Digitalis, assay of tincture of, 832*
 bodies, qualitative comparison of, 237
 circulatory changes after full therapeutic doses, 300*
 with special reference to the liver and comparison with histamine and epinephrin, 306*
 measurements in patients with rheumatic heart disease before and after administration of, 301*
 dosage in auricular fibrillation, influence of the activity of the cardiac nerves on the size of the effective dose, 788
 effect of, on the T-wave of the electrocardiogram, experimental study in human beings, 804
 on the premature auricular contraction, associated with attacks of paroxysmal auricular fibrillation, 458
 standardization, main factors of, with a new assay method, 437*
 studies in ambulatory cardiac patients, 301*
 therapy in lobar pneumonia, studies concerning, 432*
 the value in the treatment of children with rheumatic heart disease, 718*
 Dill, D. B., Boek, A. V., and Edwards, H. T., 437*
 Diphtheria, circulatory failure of, treatment of, 293*
 Dock, William, 690
 and Tainter, M. L., 300*
 Doumier, Ed., Laubry, C., Routier, D., and Walker, J., 444
 Drake, Carl B., 436*
 Drake, E. H., 834*
 Drinker, Cecil K., and Field, M. E., 439*

- DuBois, Louis, and Nyiri, W., 437*
 Ductus arteriosus, ease of primary bacterial pulmonary endarteritis, 555
 Dunning, Henry S., 565

E

- Earl, C. J. C., and Beresford, E. H., 578*
 East, C. F. T., and Bain, C. W. C., 445
 Eckels, John C., and Shoemaker, R., III, 430*
 Eddy, Howard C., and Taylor, H. P., 683
 Edwards, H. T., Boek, A. V., and Dill, D. B., 437*
 Electrocardiogram, appearance time of T-wave changes following acute coronary occlusion, 304*
 changes in myocardial ischemia, 522
 in pneumonia, 696
 clinical significance of abnormalities of, 833*
 complete inversion of Lead III of, 333
 large Q-wave in Lead III, 437*
 splintering of terminal portion of the QRS deflections, 472
 in obesity, 577*
 interpretation of the mitral deflection of the ventricular complexes of the, 637
 low voltage T-waves in, 579*
 methods of study of, and the normal, 834*
 occurrence and significance of, displaying large Q-waves in Lead III, 723
 studies in infectious diseases, 541
 use of, in study of cardiac arrhythmias, bradycardia, and tachycardia, 834*
 Electrocardiography, clinical, (book review), 721
 Electrodes, needle, value of, in electrocardiographic diagnosis, 536
 Eliason, E. L., and Wood, F. C., 581*
 Elliot, Albert H., and Nuzum, F. R., 713*
 Ellis, Lawrence B., and Weiss, S., 301*, 305*
 Ellis, Reginald, and Bramwell, C., 714*
 Endocarditis, infectious, diagnosis and treatment, (book review), 440
 pneumococcal, with early calcification and with calcareous renal emboli, 420
 streptococcus viridans in children, 434*
 Endocardium, pockets in, 584*
 Epistaxis and vomiting in rheumatic individuals, 430*
 Ernstene, A. Carlton, Blumgart, H. L., and Lawrence, J. S., 718*
 Ewing, George, Harrison, T. R., and Pilcher, C., 296*
 Eyster, J. A. E., and Kurtz, C. M., 67
 and Meek, W. J., 582*

F

- Faulkner, James M., 834*
 Feil, Harold, 778
 and Steuer, L., 472
 Feil, H. S., Katz, L. N., Moon, R. A.,
 and Scott, R. W., 522
 Feinberg, Sidney C., and Samuels, S. S.,
 255
 Fibrillation, auricular, 578*
 and flutter in metastatic growths of
 the right auricle, 434*
 as the only manifestation of heart
 disease, 183
 digitalis dosage in, 788
 effect of, on the operative risk in
 hyperthyroidism, 431*
 etiology and prognosis, 293*
 in the newly born infant, 824
 ventricular, with cardiac recovery,
 caused by carotid sinus pres-
 sure in a case of auricular
 fibrillation, 758
 Field, M. E., and Drinker, C. K., 439*
 Findlay, Leonard, MacFarlane, J. W.,
 and Stevenson, M. M., 580*
 Fishberg, Arthur M., 434*
 Fitzhugh, Greene, 430*
 Flutter, auricular, and fibrillation in
 metastatic growth of the right
 auricle, 434*
 Foramen ovale, closure of, 830*
 Foulger, John H., and McGuire, J., 536
 Fowler, W. M., and Baldridge, C. W., 83
 Freund, Hugo A., and Cooksey, W. B.,
 608

G

- Gaberman, Peter, and Brams, W. A., 804
 Gager, Leslie T., 103, 444
 Gargill, Samuel L., Blumgart, H. L., and
 Gilligan, D. R., 297*
 Gelfand, Ben., Gold, H., Hitzig, Wm.,
 and Glassman, H., 237
 Garandel, Emile, 307
 Gilligan, Dorothy Rourke, Blumgart, H.
 L., and Gargill, S. L., 297*
 Given, Thurman B., 132
 Glassman, Herman, Gold, H., Hitzig,
 Wm., and Gelfand, B., 237
 Gold, Harry, and DeGraff, A. C., 307*
 Hitzig, Wm., Gelfand, B., and Glass-
 man, H., 237
 Gordon, Harry, and Perla, D., 584*
 Graef, Irving, and De La Chapelle, C.
 E., 835*
 Graybiel, Ashton, and Sprague, H. B.,
 438*
 Grimes, Eli, 834*
 Gross, Louis, and Leslie, E., 665
 Antopal, W., and Sacks, B., 575*

H

- Hampton, A. O., Bland, E. F., and
 Sprague, H. B., 77
 Hansen, Olga J., and King, F. W., 433*
 Harrison, Tinsley R., and Pilcher, C.,
 295*
 Pilcher, C., and Clark, G., 296*
 Pilcher, C., and Ewing, G., 296*
 Calhoun, J. A., Cullen, G. E., and
 Clark, G., 582*
 Pilcher, C., Calhoun, J. A., and Cullen,
 G. E., 296*
 Harvey, Earle A., and Levine, S. A.,
 432*
 Haskins, Frank E., Chillingworth, F. P.,
 and Casey, G. U., 832*
 Hauffe, George, 306
 Heart-block, barium chloride in the
 Stokes-Adam's syndrome of,
 431*
 bundle branch, 577*
 interpretation of, by means of
 the monocardigram, 447
 partial, 375
 right, 285
 complete and relative ventricular
 tachycardia, coronary throm-
 bosis with, 820
 congenital, 289
 sino-auricular, 478
 bullet in, 430*
 congenital abnormality of, func-
 tionally two chambered heart,
 718*
 patent ductus arteriosus and pul-
 monic stenosis associated
 with subacute bacterial
 endarteritis of pulmonary
 artery, 584*
 pulmonic stenosis with late onset
 of cyanosis, 838*
 disease, (book review), 444, 445, 841
 clinical features of, (book review),
 308
 configuration of the heart in, 436*
 in children, congenital syphilis as a
 cause of, 136
 due to congenital syphilis, 132
 in general practice, 838*
 in obstetrical practice, 839*
 in the Rocky Mountain region, 264
 methods of study by the roentgen
 ray, 834*
 mitral, treatment in children, 576*
 problems associated with urinary
 retention, 578*
 rheumatic, circulatory measurements
 in patients with, before and
 after administration of
 digitalis, 301*
 digitalis, its value in the treat-
 ment of children with, 718*
 management of convalescence in,
 435*
 paroxysmal cardiac pain in
 patients with, 565

- Heart Disease, Rheumatic—Cont'd
 urobilinuria in children with, 585*
 syphilitic, certain aspects of, 715*
 examinations of, standardized procedure for microscopic studies of, 575*
 failure, buffering power of the blood and plasma, 296*
 congestive, effect of administration of dibasic potassium phosphate on the potassium content of certain tissue, 582*
 effect of overwork and other factors on potassium content of the cardiac muscle, 582*
 effect of overwork on the potassium content of skeletal muscle, 582*
 liver function in, 583*
 formed elements in urinary sediment of patients suffering from heart disease, 583*
 frequency of, effect of exposure to cold on the, of man, 830*
 potassium content of skeletal and cardiac muscle, 296*
 muscle obtained by biopsy, 296*
 respiratory exchange during and after exercise, 295*
 fluoroscopic studies of aorta and, in syphilis, 67
 in children with congenital syphilis, 128
 in old age, 835*
 mechanism of, and its abnormalities, (book review), 307
 death of, as recorded in the electrocardiogram, 743
 morbid anatomy, studies of, from patients dying with hyperthyroidism, 715*
 muscle, potassium content of, of persons dying from edematous and non-edematous conditions, 581*
 ischemia of, rôle in producing R-T deviations in the electrocardiogram, 833*
 pain, paravertebral injections of alcohol for the relief of, 840*
 pathology of, in cardiovascular syphilis, 30, 37
 in syphilitic aortic insufficiency, 56
 preservation, paraffin infiltration, 665
 pulsation of, and movements of blood, (book review), 306
 recovery of, after ventricular fibrillation, 758
 resuscitation of, by intracardiac therapy, 302*
 roentgen study of, 834*
 rupture, 578*
 size of, effect of amyl nitrite on, and the width of the aortic shadow as determined roentgenographically, 299*
- Heart, size of—Cont'd
 in goiter, a teleroentgenographic study, 575
 sound, failure in acute coronary occlusion, 577*
 influence of auricular contraction on the first sound, 438*
 status of, in myxedema, 734
 symptoms, hyperthyroidism with low metabolic rate, 730
 volume, enormous increase of, with mitral stenosis, 585*
- Henderson, Yandell, 548
 Herrick, James B., 589
 Herrmann, George, and Ashman, R., 375
 Hill, Ian G. W., 577*
 Hines, Laurence E., and Carr, J. G., 142
 Hiseock, Mabelle, Richards, D. W., and Riley, C. B., 584*
 Histamine, further observations on the circulatory action of digitalis and strophanthin with special reference to the liver and comparisons with epinephrine and, 300*
 Hitchcock, C. H., Derick, C. L., and Swift, H. L., 295*
 McEwen, C., and Swift, H. L., 433*
 Hitzig, William, Gold, H., Gelfand, B., and Glassman, H., 237
 Homans, Katharine A., Levine, S. A., and Andren, T., 430*
 Hoppe, Lewis D., and Blackford, L. M., 718*
 Horine, Emmet F., and Weiss, M. M., 121
 Hoskins, Jenner, 431*
 Hurxthal, Lewis M., 304,* 833*
 Menard, O. J., and Bogan, M. E., 575*
 Hyman, Albert S., 302*
 and Parsonnet, A. E., 431,* 577*
 Hypertension, (book review), 444
 arterial, (book review), 587
 analysis of 500 instances of, 713*
 bismuth subnitrate in the treatment of, 305*
 rational treatment of, 305*
 carbohydrate metabolism in, 717*
 essential, contributions to the problem of, 716*
 diastolic blood pressure, 839*
 nature of symptoms associated with, 716*
 treatment of, 304*
 postural, 225
 relation of, to syphilis, 121
 Hyperthyroidism, cardiac symptoms with low metabolic rate, 730
 Hypotension postural, 839*
- I
- Induration of lung, pathogenesis of, 171
 Ingraham, Ruth, and Maynard, E. P., Jr., 82
 Insulin shock and the myocardium, 575*
 Izquierdo, Jose Joaquin, 832*
 and Barcroft, J., 830*

J

- Jaffe, H., Master, A. M., and Romanoff, A., 696
Jolliffe, Norman, 436*

K

- Kaiser, Albert D., 303*
Katz, L. N., and Siegel, M. L., 672
and Wallace, A. W., 438, 833*
Feil, H. S., Moore, R. A., and Scott, R. W., 522
Kelly, Luther W., 285
King, Frances W., and Hansen, O. S., 433*
Koch, Eberhard, 720
Korns, Horace Marshall, 423
Kurtz, Chester M., and Eyster, J. A. E., 67

L

- Larson, Ralph M., and Trimble, W. H., 555
Laubry, Charles, Routier, D., Walser, J., and Doumier, E., 444
Lawrence, John S., Blumgart, H. L., and Ernestene, A. C., 718*
Leech, Clifton B., 434*
Lennox, William G., and Leonhardt, E., 304*
Leonhardt, Erna, and Lennox, W. G., 304*
Leslie, Eugenie, and Gross, L., 665
Levine, Samuel A., 116
and Harvey, E. A., 432*
Andren, T., and Homans, K. A., 430*
Levy, Robert L., 579*
and Moore, R. L., 840*
Lewis, Sir Thomas, 721
Lloyd, Wray, 438, 504
Long, Charles-Francis, and Arnett, J. H., 838*
Lungs, collapse, influence of on electrocardiogram, 433*

M

- MacFarlane, James W., Findlay, L., and Stevenson, M. M., 580*
MacLeod, A. Garrard, Wilson, F. N., and Barker, P. S., 637
McClure, William B., and Carr, J. G., 824
McCrudden, Francis H., 586*
McCulloch, Hugh, 136
McDonald, R. H., 561
McEachern, Donald, and Rake, G., 715*
McEwen, Currier, Hitchcock, C. H., and Swift, H. F., 433*
McGuire, Johnson, and Foulger, J. H., 536
McIlroy, Dame Louise, and Rendel, O., 839*
McKinlay, C. A., 436*
McMeans, J. W., 42
Maher, Chauncey C., 37
Mann, Hubert, 447

- Margolies, Alexander, and Wolferth, C. C., 438*
Margolis, Harry M., Zielessen, F. D., and Barnes, A. R., 349
Marathon runners, observations on the circulatory mechanism in, 714*
Martland, Harrison S., 1
Masters, Arthur M., 579*
Romanoff, A., and Jaffe, H., 696
Maynard, Edwin P., Jr., and Ingraham, R., 82
Meek, Walter J., and Borman, M. C., 831*
and Eyster, J. A. E., 582*
Menard, O. J., Hurxthal, L. M., and Bogan, M. E., 575*
Mignot, R., Sergent, E., and Turpin, R., 440
Mitchell, A. Graeme, and Selkirk, Theodore K., 837*
Mitral valve, stenosis, enormous increase of heart volume with, 585*
experimental, acute, cardiodynamic effects of, 672
experimental, observation on circulation in, 833*
observation on, among Chinese, 431*
Monocardiogram, interpretation of bundle-branch block by means of, 447
Moon, R. A., Feil, H. S., Katz, L. N., and Scott, R. W., 522
Moon, V. H., and Stewart, H. L., 583*
Moore, Adams D., Previtali, G., and Nicholson, G. H. B., 128
Moore, Joseph Earle, and Danglade, J. H., 148
Moore, Norman S., and Stewart, H. J., 583*
Moore, Richmond L., and Levy, R. L., 840*
Morenas, Leon, and Pic, A., 306
Morris, Roger S., 730
Morton, John J., and Scott, W. J. Merle, 298,* 719*
Moschowitz, Eli, 171
Myocarditis, interstitial acute, 238
and insulin shock, 575*
chronic, a clinical and pathological study, 430*
isolated, acute, 835*
Myocardium, in yellow fever, 483, 504
ischemia of, electrocardiographic changes in, 522
Myxedema, status of heart in, 734

N

- Nicholson, Gertrude H. B., Previtali, G., and Moore, A. D., 128
Niles, Walter L., and Wyckoff, J., 432*
Node, sino-auricular, boundaries of, in the human heart, 585*
rhythm subsequent to destruction by radon of, 831*

- Noel, William M., and Schwentker, F. F., 293*
 Nuzum, Franklin R., and Elliot, A. H., 713*
 Nye, Robert N., and Parker, F., Jr., 294*
 Nyiri, William, and DuBois, L., 437*

O

- Oatway, William H., and Middleton, W. S., 575*
 Obesity, electrocardiogram in, 577*
 O'Hare, James P., 586*
 Olcott, Charles T., 713*

P

- Packard, Frederic, Jr., and Wechsler, H. F., 281
 Padilla, T., and Cassio, P., 721
 Palmer, George A., 230
 Palmer, Harold D., and Boswell, C. H., 717*
 Palmer, Robert S., 304,* 586*
 Pardee, Harold E. B., 437*
 Parker, Frederick, Jr., and Nye, R. N., 294
 Parkinson, John, and Bedford, D. Evan, 579*
 and Campbell, M., 578*
 Parsonnet, Aaron E., and Hyman, A. S., 431,* 577*
 Patten, Bradley M., 182, 830*
 Pericarditis effusion, 581
 of unknown etiology necessitating repeated paracentesis, 561
 rheumatic in childhood, 580*
 Pericardium, absorption from cavity of, 439*
 cyst of, 710
 Peritonitis, rheumatic, 581*
 Perla, David, and Gordon, H., 584*
 Pic, Adrien, and Morenas, L., 306
 Pilcher, Cobb, Calhoun, J. A., Cullen, G. E., and Harrison, T. R., 296*
 Clark, G., and Harrison, T. R., 296*
 Harrison, T. R., 295*
 and Ewing, G., 296*
 Powers, J. H., and Bowic, M. A., 833*
 Pneumonia, electrocardiographic changes in, 696
 studies concerning digitalis therapy in, 432*
 Powers, John H., Pilcher, C., and Bowic, M. A., 833*
 Pratt, Joseph H., and Ayman D., 716*
 Premature contractions, auricular, associated with paroxysmal auricular fibrillation, effects of digitalis on, 458
 ventricular, effect of, on the auriculo-ventricular conduction time, of the next auricular impulse, 416
 Previtali, Guiseppe. Nicholson, G. H. B., and Moon, A. D., 128

- Proger, Samuel H., 577*
 Pulmonary artery, thrombosis progressive, 717*
 valve, stenosis, acquired rheumatic, 568

R

- Raab, W., 716*
 Rake, Geoffrey, and McEachern, D., 715*
 Ramsay, Robert E., and Crumrine, R. M., 838*
 Reid, William D., 91, 585,* 838*
 Reifenshtein, Edward C., and Allen, E. G., 274
 Reinhart, Alfred S., 836*
 Rendel, Olive, and McIlroy, Dame L., 839*
 Rheumatic fever, antistreptococcus serum treatment of patients with, 433*
 evolution of the clinical concept of, 836*
 experimental lesions in dogs and in rabbits, 583*
 factor of infection in the state of, (book review), 842
 factors favoring the onset and continuation of, 625
 in adult Porto Rican immigrants, 836*
 in childhood, 434*
 intravenous vaccination with hemolytic streptococci, 837*
 involvement of coronary arteries in, 576*
 vaccine therapy in, experimental, relation to and possible basis for, 836*
 Richards, Dickinson W., Riley, C. B., and Hiscock, M., 584*
 Riecker, H. H., and Upjohn, E. G., 225
 Riley, Constance B., Richards, D. W., and Hiscock, M., 584*
 Romanoff, A., Masters, A. M., and Jaffe, H., 696
 Rösler, Hngo, 834*
 and White, P. D., 768
 Routier, Daniel, Laubry, C., Walser, J., and Donnier, E., 444

S

- Sacks, Benjamin, Gross, L., and Antopal, W., 575*
 Salyrgan as a diuretic, 438*
 Samuels, Saul S., and Feinberg, S. C., 255
 Sanders, Audley O., 820, 839*
 Sanders, C. A., and Schwab, E. H., 838*
 Saphir, Otto, 584*
 and Scott, R. W., 56
 Schmitz, Herbert W., 585*
 Schwab, Edward H., 404
 and Sanders, C. B., 838*
 Schwartz, Sidney P., 458
 and Shilling, D., 568
 Schwentker, Francis F., and Noel, W. M., 293*

- Selar, Meyer, 289
 Scott, L. C., 581*
 Scott, R. W., and Saphir, O., 56
 Feil, H. S., Katz, L. N., and Moon, R. A., 522
 Scott, W. J. Merle, and Morton, J. J., 298,* 719*
 Selkirk, Theodore K., and Mitchell, A. G., 837*
 Sergeant, E., Mignot, R., and Turpin, R., 440
 Sheldon, Wilfrid, 434*
 Shilling, David, and Schwartz, S. P., 568
 Shoemaker, Robert, III, and Eckels, J. C., 430*
 Shookhoff, Charles, 758
 and Taran, L. M., 541
 Siegel, Mortimer L., and Katz, L. N., 562
 Simpson, J. Levy, 309
 Slater, Solomon R., 576*
 Smith, Arthur L., 436*
 Sosman, Merrill, 834*
 Sprague, Howard B., 585*
 and Graybiel, A., 438*
 Hampton, A. O., and Bland, E. F., 77
 Sproull, John, 834*
 Steel, David, 59
 Steuer, Leonard, and Feil, H., 472
 Stevenson, Mary M., Findlay, L., and MacFarlane, J. W., 580*
 Stewart, Harold J., and Moore, N. S., 583*
 Stewart, H. L., and Moon, V. H., 583*
 Sloan, G., 578*
 Stieglitz, Edward J., 305,* 587
 Strauss, Herman A., and Brans, W. A., 299*
 Strax, Philip, and DeGraff, A. C., 807
 Streptococcus, hemolytic, intravenous vaccination with, 837*
 experimental inflammation in normal, immune and hypersensitive animals, 294*
 localization of, in the tissues of rabbits, 294*
 non-hemolytic, modes of sensitization in rabbits, 295*
 serum treatment of patients with rheumatic fever, 433*
 Strophanthus, further observation on the circulatory action of digitalis and, with special reference to the liver and comparison with histamine and epinephrine, 300*
 Suprarenalin, further observation on the circulatory action of digitalis and, with special reference to the liver and comparison with histamine and epinephrine, 300*
 Sutton, Lucy Porter, 581*
 and Wyckoff, J., 718*
 Swift, Homer F., 625
 and Wilson, M. G., 837*
 Derick, C. L., and Hitchcock, C. H., 295*
 Hitchcock, C. H., and McEwen, C., 433*
 Sympathectomy, observation on the surface capillaries in man following cervicothoracic sympathetic ganglionectomy, 298*
 Syphilis, cardiovascular, diagnosis of, 91
 gross pathology of heart in, 30
 study of course of, 113
 treatment of, 148
 principles underlying, 157
 use of intravenous arsenicals in treatment of, 142
 congenital, as a cause of heart disease, 136
 clinical heart findings in children with, 128
 heart disease in children due to, 132
 early, electrocardiograms and tele-roentgenograms in, 82
 fluoroscopic studies of the heart and aorta in, 67
 localization of virus of, in the aorta, 42
 of the aorta, 1
 microscopic pathology, 37
 relation of, to hypertension, 121
 rôle of, in etiology of angina pectoris, coronary arteriosclerosis and thrombosis and of sudden cardiac death, 163
 Systole, electrical, duration of, as an index of myocardial efficiency, 690
- T
- Tachycardia, ventricular paroxysmal, 578*
 observation on the etiology and treatment of, 404
 relative and complete heart-block, coronary thrombosis with, 820
 Tainter, M. L., and Dock, W., 300*
 Taran, Leo M., and Shookhoff, C., 54
 Taussig, Helen B., 585*
 Taylor, Howard P., and Early, H. C., 683
 Temperature, relation of, to pulse rate of frog, 830*
 Theisen, Harold, Wiggers, C. J., and Williams, H. A., 299*
 Thromboangiitis obliterans, the heart in, 255
 Thrombus, mural, study of, 432*
 Thyroid, hyperthyroidism, effect of auricular fibrillation on the operative risk in, 431*
 study of the morbid anatomy of hearts from patients dying with, 715*
 size of the heart in goiter, 575*

- Tension, arterial, effect of intrathoracic pressure on, 834*
 capillary, a new method for the clinical determination of human, 807
 Tonsillectomy, evaluation of the results of, 837*
 results of, 303*
 Trehwella, Arthur P., and Yater, W. M., 840*
 Trimble, W. H., and Larson, R. M., 555
 Tuberculosis, cardiovascular, (book review), 306
 electrocardiographic and roentgenographic studies of the heart in, 433*
 Tnug, C. L., 734
 Turner, Kenneth B., 743
 Turpin, R., Sergeant, E., and Mignot, R., 440

U

- Upjohn, E. G., and Riecker, H. H., 225
 Urine retention, problems of cardiac disease associated with, 578*
 sediment, formed elements in, of patients suffering from heart disease with particular reference to the stage of heart failure, 583*
 Urobilinuria in children with rheumatic heart disease, 585*
 Uttal, Joseph, 426

V

- Valentine, Eugenia, and Van Meter, M., 294*
 Van Meter, Martha, and Valentine, E., 294*
 Vasomotor system, contribution to the problem of essential hypertension, 716*
 instrumental methods in the study of disease of, 309
 measurement of sympathetic vasoconstrictor activity in the lower extremities, 298*
 reflex regulation of the circulation, (book review), 720
 Veins of the heart, reversal of flow in, 206
 Vena cava, superior, arteriovenous aneurysm between aorta and, 281

- Venous pressure, studies on, 582*
 Verzar, F., and Barcroft, J., 830*
 Viko, L. E., 204
 Vomiting and nosebleed in rheumatic individuals, 430*

W

- Wallace, A. W., and Katz, L. N., 478, 833*
 Walser, J., Landry, C., Rontier, D., and Dommer, E., 444
 Warthin, Alfred Scott, 163
 Wechsler, H. F., and Packard, F., Jr., 281
 Weiss, Morris M., and Horine, E. F., 121
 Weiss, Sonna, 586*
 and Ellis, Laurence B., 301*, 305*
 White, Paul D., 841
 and Rösler, H., 768
 and Bland, E. F., 333
 and Balboni, G. M., 585*
 Wiggers, Carl J., and Theisen, H., and Williams, H. A., 299*
 Wile, Udo J., 157
 Williams, H. A., Wiggers, C. J., and Theisen, H., 299*
 Willius, Fredrick A., 113, 723, 835*
 Willner, Otto, 431*
 Wilson, Frank N., MacLeod, A. G., and Barker, P. S., 637
 Wilson, May G., and Swift, H. F., 837*
 Wisnufsky, Max, and Byron, C. S., 717*
 Wolferth, Charles C., and Margolis, A., 438*
 Wood, Francis C., 580*
 Wood, Francis C., and Eliason, E. L., 581*
 Wolferth, C. C., 580*
 Wyckoff, John, and Niles, W. L., 432*
 and Sutton, L. P., 718*
 Yater, Wallace M., 710
 and Trehwella, A. P., 840*
 Yellow fever, experimental, myocardial function in, 483*
 myocardial lesion in, 504

Z

- Zeisler, Ernest Bloomfield, 416
 Ziellessen, Frederick O., Margolis, H. M., and Barnes, A. R., 349

VALUABLE SUGGESTIONS FOR CONTRIBUTORS

TO

THE AMERICAN HEART JOURNAL

"The four rules for the preparation of an article will then be: (1) Have something to say; (2) Say it; (3) Stop as soon as you have said it; (4) Give the paper a proper title."¹

Let your phraseology express one meaning and one only. Be clear.²

Manuscript.—Manuscripts should be typewritten, with wide margins, and double spaced, on one side of paper 8½ by 11 inches in size. The original copy should be sent to the editor of the journal and the carbon copy retained by the author. Number the sheets consecutively, beginning with the title page. Put your name and address on the manuscript.

Illustrations.—Illustrations should be clear, preferably pen-and-ink drawings. Of photographs send a good print rather than a negative. Have lettering parallel to the bottom and top margins, and of sufficient size to be clear if cut is to be reduced. Tracings should be in black-and-white; avoid colors. Write your name on back of each picture; number them in one series (Fig. 1, etc.) to the end, and indicate in margin of the manuscript about where each is to be printed. See that text references and "figures" correspond. Legends for illustrations should be written on a separate sheet.³

Bibliographic References.—Give only references actually consulted. If an article is known only through an abstract give reference to the abstract in addition to that of the source. References are printed to be of help in further reading; therefore they must be complete, concise, and correct. Follow the style of the "Quarterly Cumulative Index." Be conservative in the use of abbreviations.

Arrangement.—As authors are quoted in the text give each a number in the order of citation, and number the bibliographic reference with the same number. Arrange the references in a list at the end of the article in the order of the numbers (see below), or arrange items in alphabetical order according to last names of authors, and distinguish between articles by the same author by the use of the date after his name in the text.

Footnotes.—Footnotes should be placed at bottom of each page. Indicate footnotes by an asterisk (*).

Final Reading.—Let some one other than the author read the manuscript with these directions in mind.

Shipment.—Send manuscript flat, postage paid, to the editor, Dr. Lewis A. Conner, 333 East 68th Street, New York, N. Y.

Proof Reading.—Read carefully, with special attention to spelling of names and bibliographic data. Make corrections *in the margin* only with lines drawn from the revision to the point of change in the text. Answer queries in the proof by making correction or crossing out the query. Verify your references from the sources, not from your carbon copy.

References. (Read these.)

¹Billings, J. S.: Our Medical Literature, Trans. VII Intern. Med. Congress, Lond., 1: 51-70, 1881.

²Mayer, Emil: Medical Literature and Its Preparation. Med. Record, N. Y. 87: 1019-1021, 1915.

³Allbutt, T. C.: Notes on the Composition of Scientific Papers. London, Macmillan, 1904.

McCrae, Thomas: The Use of Words. Jour. A. M. A., Chic., 65: 135-139, 1915.

⁴Suggestions to Medical Authors, issued by the A. M. A. Press, Chic., A. M. A.

